

Carcinoma Of The Urinary Bladder In Maiduguri: The Schistosomiasis Connection

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Citation

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Abstract

Background: A prospective study of all patients admitted to the University of Maiduguri Teaching Hospital (UMTH), with a provisional diagnosis of carcinoma of the urinary bladder in the six year period between January, 2001 and December, 2006. The object of this investigation was to determine the relationship between schistosomiasis and carcinoma of the urinary bladder in Maiduguri, North East of Nigeria.

Method: All the patients were assessed clinically, and investigated by urine cytology, cystoscopy and biopsy for histology. Those confirmed at histology to have carcinoma were analyzed for age, gender, occupation, history of Schistosomiasis, tobacco use, pathological type, presence or absence of schistosoma ova in the specimen, stage of the disease, complications, treatment and outcome.

Results: All but 13 of the 65 confirmed cases were males, giving a male to female ratio of 4 to 1. Squamous cell carcinoma (SCC) of the bladder (n=46) was significantly commoner than transitional cell carcinoma (TCC) cases (n=15), in those with past history of Schistosomiasis ($p < 0.001$), with a Relative Risk (RR) of 4.06. Also 65.2% of SCC showed Schistosomiasis in the histology specimen compared with 13.3% of TCC cases ($P < 0.001$)

Four patients had undifferentiated carcinoma, 3 (75%) of which showed Schistosoma ova in their specimen.

Patients with SCC were significantly younger (45.26 +/- SD13.5years) than those with TCC ($P < 0.001$).

Our patients were mostly farmers of low socio-economic class. Most presented with advanced disease, thus treatment was mostly palliative and the outcome quite poor.

Conclusion: This result clearly shows that carcinoma of the bladder in Maiduguri, North East of Nigeria, is mainly SCC and strongly associated with Schistosomiasis. Therefore, a deliberate policy and effort to control Schistosomiasis in this region will lead to a reduction in the incidence of bladder cancer and the attendant morbidity and mortality.

INTRODUCTION

Bladder cancer is the second most common genito-urinary neoplasm after prostate cancer. It is more common in the industrialized communities and in Caucasians than in Blacks. In the western society, most patients are over 50 years old with a peak prevalence among 60-70 years old and a male to female ratio of 3:1^{1,2}.

Ninety percent of bladder malignancies are transitional cell tumours (TCC), reflecting their origin from the transitional cells that line the bladder^{2,3}. Squamous cell carcinoma (SCC) comprises approximately 6-8% of bladder tumours, with only 2% being adenocarcinoma. However, in Schistosoma endemic areas, SCC constitutes as high as 44-82% of bladder cancer⁴. In fact, carcinoma of the

urinary bladder is the most common malignancy among Egyptians⁵

There are several complications of chronic urinary bladder schistosoma infection and bladder cancer associated with Schistosomiasis is a major cause of morbidity and mortality in endemic areas. A survey of urinary Schistosomiasis carried out in Maiduguri in 1983 shows that a sizeable population of the North East of Nigeria is at risk of developing urological complications from Schistosomiasis^{6,7}. The incidence of Schistosomiasis is so common in some communities that young men regard the bloody urine passed at some stage of the disease as a sign of attainment of manhood. In effect, no medical advice is sought at this stage of the disease, and no attempt is made at prevention.

Presently, carcinoma of the urinary bladder constitutes 5.5% of all adult cancers seen here⁸. Most of our patients give a positive history of Schistosomiasis, and histology commonly confirms a diagnosis of SCC or anaplastic carcinoma. Schistosoma ova are a frequent finding on the histology specimen. Reports from other parts of the country show quite a significant influence of Schistosomiasis on the histological pattern of urinary bladder cancer, albeit to varying degrees^{9,10,11,12}. However, there has not been any prospective study for any environmental associations here in Maiduguri. It is therefore our hope that by this prospective study, an accurate assessment of the relationship between Schistosomiasis and carcinoma of the urinary bladder in Maiduguri will be made.

PATIENTS AND METHODS

The study was conducted between January 2001 and December 2006. The approval of the ethical committee was obtained before the study.

All patients admitted to UMTH with a provisional diagnosis of carcinoma of the urinary bladder were recruited into the study. These were assessed clinically and investigated. Patient characteristics included age, sex, occupation, history of Schistosomiasis and smoking of tobacco. Urine microscopy for Schistosoma ova and urine cytology were done. All cases had a cystoscopic evaluation with biopsies of any suspicious tumoural areas and random bladder mucosa sampling for histological confirmation of carcinoma. The presence or otherwise of Schistosoma ova in the specimen was noted.

If surgery was planned, biopsies of bladder wall were taken along with the tumour or part of the tumour. All pathological specimens were examined by the consultant pathologist. The outcome of treatment and any morbidity or mortality was recorded during patient follow-up.

Collected data was tabulated. Values were expressed as mean +/- standard deviation (M +/- SD) and Chi-square test used to compare means. The Chi-square test and the relative risks were used to examine the association of history of Schistosomiasis and development of SCC of the bladder. P-value of less than 0.05 was taken as level of statistical significance. Epi-info statistical soft-ware version 6 was used for data analysis.

RESULTS

Sixty-five cases were enrolled who had urine cytology collected, as well as cystoscopy and examination under

anaesthesia, with histological confirmation of malignancy. Secondary carcinoma from either the prostate or the rectum were excluded. Of the 65 confirmed cases, 46(70.8%) were SCC, 15(23%) were TCC, 4 (6.2 %) were undifferentiated carcinoma (Fig. 1).

Figure 1

Figure 1: Pie chart showing distribution of the histological types of bladder cancer

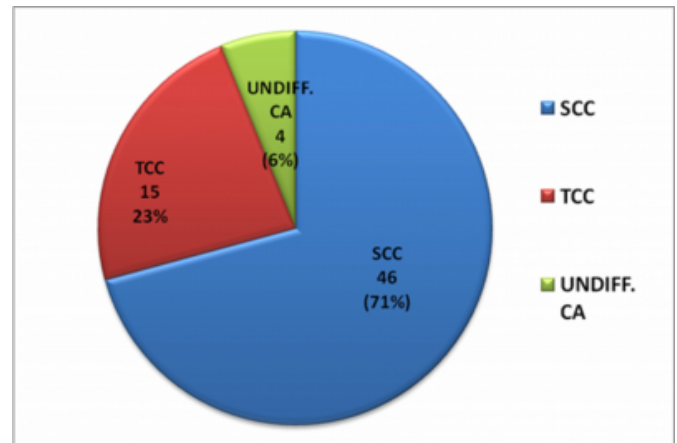


Figure 2

Table 1: Age distribution and histological types of bladder cancer.

Age range	Number of cases of bladder cancer	SCC	TCC	Undifferentiated Carcinoma
21-30	8	8		
31-40	12	12		
41-50	14	12	2	
51-60	18	10	6	2
61-70	13	4	7	2
Total	65	46	15	4

All but 13 of the 65 cases seen were males giving a male to female ratio of 4 to 1. The age of patients seen in the study ranged from 21 to 70years, with a peak age incidence between 51 and 60 years (Table 1).

Figure 3

Figure 2: Bar chart showing age distribution of cases of SCC and peak age incidence

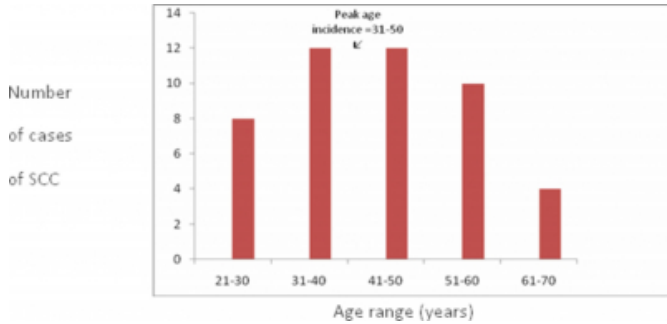
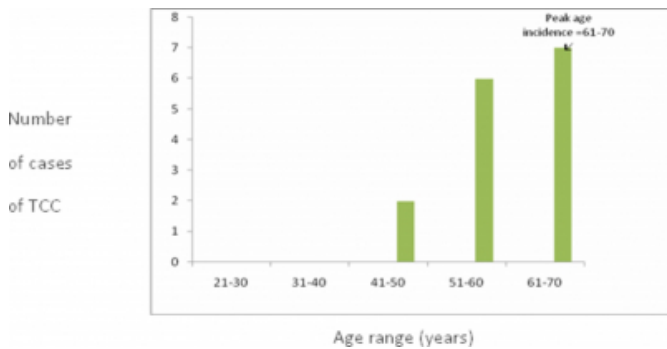


Figure 4

Figure 3: Bar chart showing distribution of cases of TCC and peak age incidence



The peak age for SCC was 31 to 50 years. The peak age for TCC cases was 61 to 70 years (Fig. 2 and 3). The occurrence of SCC at a young age (45.26 +/- SD 13.5 years) compared to TCC (58.57 +/- 10.50 years) is statistically significant (p < 0.001).

Most of the patients were of low socio-economic class. Fifty-one (78.5%) patients were farmers, 7 were civil servants, 5 patients and 2 patients were petty traders and artisans respectively. None worked in a dye, rubber or chemical industry. Three patients smoked 1-9 sticks of cigarettes per day for over 25 years. Two patients only admitted to drinking 1-2 bottles of larger beer per day for over 10 years. Forty-seven (72.3 %) of the patients had a history of Schistosomiasis infection. Of these 42 (89.4%) had SCC, 3 (6.4%) had undifferentiated carcinoma while 2 (4.3%) had TCC. Eighteen (27.7 %) patients did not give a positive history of Schistosomiasis. Of these, 13 (72.2%) had TCC, 4 (22.2%) had SCC, and 1 (5.6%) had undifferentiated carcinoma (Table 2).

Figure 5

Table 2: Types of carcinoma of urinary bladder and history of Schistosomiasis

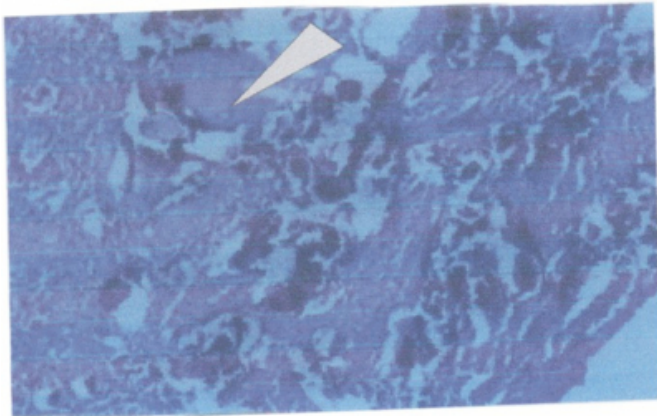
	SCC	TCC	Undifferentiated Carcinoma	Total
Past history of Schistosomiasis	42	2	3	47
No history of schistosomiasis	4	13	1	18
Total	46	15	4	65

The commonest symptoms were haematuria, which occurred in all the patients (100%), frequency of micturition 60 (92.3%), necrotic materials in urine 59 (90.8%), poor urine stream 54 (84.6%), urgency 47 (72.3%), and weight loss 46 (70.8%). Major signs include cachexia in 42 (64.6%), palor in 44 (67.7%), and palpable bladder mass in 53 (81.5%). Twenty-one patients (32.3%) presented at different stages of obstructive uropathy with weakness, vomiting, dehydration, altered sensorium, facial puffiness, lower limb swelling and uraemic frost. Two male patients presented with recto-versical fistula (RVF). One female patient presented with vesico-vaginal fistula (VVF).

Fourty one (63%) had a hematocrit of less than 30%. Urine cytology was positive for malignancy in 59 (90.8%); there was no case of false positive result (specificity = 100%). Urine culture showed infection in 37 (56.9%), of which E. coli was the commonest infecting organism in 26 (70.2%) cases. Abdominal ultrasound showed a bladder mass in all cases (100%), upper urinary tract obstruction in 30 (65.2%) of SCC, 6 (42.8%) of TCC, and 2 (50%) of undifferentiated carcinoma. Abdominal ultrasound also showed liver metastases in 2 cases, of which one was SCC and one undifferentiated carcinoma. Chest X-Ray showed cannon ball metastases in the lungs of two patients with SCC. Intravenous urogram showed non functional unilateral kidney in 7 cases with SCC and 2 cases with TCC. Biopsy specimen was confirmatory of malignancy in all cases under study and showed the histological pattern.

Figure 6

Figure 4: Section of bladder mass showing numerous calcified schistosomal ova (purple) with focal areas of sheets of malignant Squamous epithelium (white arrow). H&E X33 (Model: Olympus Vanox T AH-2)



There were associated Schistosoma ova in 53.8% of specimen, with much greater local load of ova in SCC cases (Fig.4). Of the 46 cases of SCC, 30 (65.2%) had Schistosoma ova in the biopsy specimen. Of the 15 cases of TCC, 2 (13.3%) had Schistosoma ova in the specimen, while 3 (75%) cases of undifferentiated carcinoma showed ova in the specimen (Table 3). SCC cases associated with Schistosoma ova in the specimen were significantly higher than cases of TCC (P=0.001).

Figure 7

Table 3: Correlation between different histological types of bladder cancer and presence of Schistosoma ova in the specimen.

Histological type	Number of cases	Number associated with Schistosomiasis ova in the specimen
SCC	46	30 (65.2%)
TCC	15	2(13.3%)
Undifferentiated Carcinoma	4	3(75%)
Total	65	35 (53.8%)

The clinical stage was assessed by bimanual pelvic examination under anaesthesia. Fourty (61.5%) had a fixed hard bladder mass (T₄), 13 (20%) had a palpable but mobile bladder mass (T₃), and 12 (18.5%) had bladder induration but no palpable bladder mass (T₂). No case was categorized as T₁ disease. Bladder lesions were observed by pelvic ultrasound scan and at cystoscopy in all cases, and their diagnosis confirmed by biopsy and histology.

Thirty five (53.8%) had varying degrees of anaemia requiring blood transfusion. Those who had urinary tract infection were treated with antibiotics based on sensitivity. Seven patients had dialysis as part of resuscitation measure.

Fourteen (21.5 %) patients underwent surgical operation. Of these 12 had a partial cystectomy and two had a total cystectomy. To qualify for surgery was the patient needed to be fit with a potential for total resectability. Twenty-one patients were referred for radiotherapy.

Thirty-two (49.2%) of the patients died of advanced disease in the hospital; 33 (50.8%) were discharged to out-patient follow-up. Overall mortality cannot be determined because most patients defaulted at follow-up.

DISCUSSION

The result shows a preponderance of squamous cell carcinoma (SCC), over transitional cell carcinoma (TCC), 46 (70.8 %) versus 15 (23 %), respectively. This is a reversal of the figures commonly quoted from the western world (90% for TCC versus 6-8 % for SCC) where Schistosomiasis is not endemic and therefore not a significant factor in the aetiology of bladder cancer³. This result is in concordance with reports on pathological pattern of bladder cancer from Schistosoma endemic regions and countries^{4,5} Reports from other parts of Nigeria also points to quite significant influence of Schistosomiasis on the distribution of the different pathological types of bladder cancer, albeit to a lesser extent when compared to our result^{9,10,11} Thomas et al¹¹ highlighted a changing trend at Ibadan, South Western Nigeria, with a rise in the frequency of TCC (44.9%) relative to SCC when compared to previous report. This was attributed to changing environmental and socio-economic factors.

In this report 89.4% of SCC and 4.3% of TCC had a past history of Schistosomiasis. The history of Schistosomiasis is therefore strongly associated with the development of SCC (P < 0.001; Relative risk 4.06). There was also a significantly higher proportion of SCC specimen with density of Schistosoma ova (65.2%) compared to 13.3% for TCC (P = 0.001). The development of SCC is highly associated to Schistosomiasis (fig. 4), unlike in the western world where SCC is often reported in relation to bladder stone, bladder diverticulum, or prolonged bladder catheterization.

It would also appear that the history of Schistosomiasis is significant in the development of undifferentiated carcinoma (75%), though the case load (only 4 cases) is too few for any statistical significance. This therefore needs further study.

The causal relationship between urinary Schistosomiasis and bladder cancer was first reported by Ferguson¹³ in 1991.

Since then, the role of *Schistosoma haematobium* in the development of bladder cancer has been widely studied. Available data support the postulate that *Schistosoma haematobium* supplies the proliferative stimulus (i.e. promotional) necessary to accelerate the development of detectable tumours from latent foci produced by exposure to bladder carcinogen ^{14,15,16,17}

There was a high rate of co-existent urinary tract infection (56.9%) in this study. This phenomenon is corroborated by studies in Egypt and South Central Africa which showed that bacterial infection in the urinary bladder is a common complication of bilharzial bladder syndrome ^{18,19,20}. Many bacteria are known to contain enzymes capable of reducing urinary nitrates to nitrites and then nitrosating secondary and tertiary amines to nitroso compounds. These N-nitroso compounds including nitrosamines and nitrosamides are well known carcinogens for the urinary bladder ^{21,22,23}. Hence *Schistosoma haematobium* is also indirectly involved in the initiation by exposing the bladder to bacterial infection which in turn generates carcinogens from urinary nitrates.

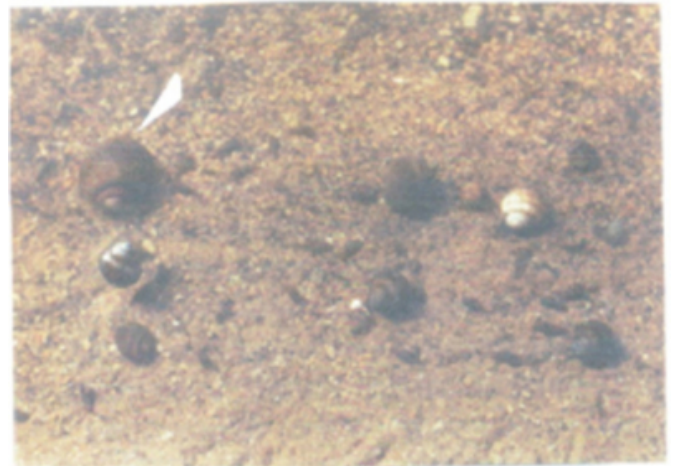
Cases of SCC occurred at a significantly younger mean age of 45.26 years compared to cases of TCC with mean age of 58.57 years ($P= 0.001$). This is consistent with reports from elsewhere with Schistosomiasis endemicity ^{5,14,15,16,17}. This variation in the epidemiology of bladder cancer is significant in that SCC mediated by Schistosomiasis affects the younger, able bodied workforce of the society and bread winners of the homes. The economic impact on the society at large is tremendous and cannot easily be assessed.

The result shows a male to female ratio of 4 to 1. The male preponderance agrees with other reports. It may be that males are generally more exposed to the environmental or occupational hazards associated with bladder cancer.

Most of the patients seen in this study are of low socio-economic class. 78% of the patients were farmers. This is quite significant and SCC of the bladder can therefore be regarded as an occupational hazard of farming in the North East region of Nigeria. The various dams and irrigation projects embarked upon in this area during the late seventies and early eighties for the benefit of the farmers has been shown to promote the proliferation of Schistosomiasis (fig.5).

Figure 8

Figure 5: Picture showing cluster of snails at the shallow bank of Alau Dam. The *Bulinus* species (white arrow) which is the intermediate host for *S. haematobium* flourishes in the clear freshwater provided by the Dam



Most patients in this study presented late. Fifty-three (81.5%) had a palpable hard bladder mass (T3-4 disease). Severe anaemia, dehydration and wasting were also common features. Most of these patients therefore required resuscitation with intravenous fluids, blood transfusion and control of infections. Unfortunately, that was all the many inoperable cases could get. Active haematuria was treated by bladder irrigation with normal saline and by treating any infection, often with good effect. Uraemia was treated by continuous bladder drainage, rehydration, and dialysis. Tube ureterostomy or palliative uretero-sigmoidostomy which was earlier done here on cases with ureteral obstruction by unresectable tumour, has mostly been abandoned because of poor results. None of that was therefore done during this course of this study. This is in accordance with the observation of Lawani et al. that ureteric transplantation alone (without cystectomy) adds to the misery of the patient ²³.

Late presentation is a common problem with bladder cancer in this environment. This is because most patients first seek native unorthodox treatment for their problems and waste vital time when the disease can be diagnosed and treated at an early stage. Missed diagnosis of early cases may also be contributory. Osegbe DN and Amaku EO ¹¹ stressed the need for early and thorough investigation of haematuria. Late presentation and poor general health condition of the patients with severe anaemia, wasting and varying degrees of uraemia, account for the low rate of surgical intervention in our patients. Treatment was therefore mostly palliative. The poor prognosis of the late presentation cannot be over

emphasized. However, the accurate mortality rate cannot be assessed because most patients were lost to follow up. Follow up is a real problem in Nigeria, attributable to illiteracy and poverty as most of the patients are of low socio-economic class.

CONCLUSION

This study shows clearly that carcinoma of the urinary bladder in Maiduguri is predominantly of the squamous cell type and is strongly associated with schistosomiasis. Therefore, a deliberate policy and effort by government and agencies to control schistosomiasis in this sub-region will ultimately decrease the incidence of carcinoma of the urinary bladder, with its attendant morbidity and mortality. Such primary prevention efforts may include public health education to control of snail intermediate host, to provide portable water supply, and to possibly treat the population at risk with mass chemotherapy. Secondary prevention interventions include health education to improve health seeking behavior of the populace and early and thorough investigation of haematuria to diagnose bladder cancer at an early stage.

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