Schistosomiasis and Carcinoma of the Bladder in Zambia

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SUMMARY
Carcinoma of the bladder is the third most important malignancy seen in Zambia, accounting for nearly 9% of all malignancies seen in the Department of Pathology at the University of Zambia. A review of 217 cases of carcinoma of the bladder seen in the department over a 5-year period revealed a preponderance of well-differentiated squamous cell carcinoma (75%). Of the 217 cases, 65% had concomitant schistosomiasis. These tumours tended to occur in a younger age group than that reported from England and North America. The pattern of pathology conforms with that reported from other parts of Africa with hyperendemic and endemic schistosomiasis. The aetiological role of schistosomiasis in bladder cancer is critically examined.


Carcinoma of the bladder is the third commonest cancer in Zambia. Concomitant Schistosoma haematobium infection is present in a high proportion of the patients. Schistosomiasis is focally endemic over large areas of Zambia, and both species, S. haematobium and S. mansoni, are prevalent. In common with the pattern of pathology described in other hyperendemic and endemic areas of S. haematobium, carcinoma of the bladder in Zambia afflicts a younger age group than in non-schistosomal areas and is predominantly a well-differentiated keratinising squamous type with a much higher incidence of S. haematobium infection than in the general population.

The association between urinary schistosomiasis and cancer of the bladder is well documented and the aetiological significance of schistosomiasis in bladder cancer has been the subject of much controversy.

This study is a review of all cases of carcinoma of the bladder seen in this department during a 5-year period. It is also a study of the association between bladder cancer and S. haematobium in Zambia. While similar studies have been done in most areas where schistosomiasis is endemic, this is the first such study in Zambia.

The possible aetiological role of schistosomiasis in bladder cancer is examined in the light of the Zambian experience and that reported by previous authors.

MATERIALS AND METHODS
The Department of Pathology and Microbiology of the University of Zambia provides diagnostic histopathological services for the University Teaching Hospital, Lusaka, and for hospitals in the central, southern, western and eastern provinces of Zambia. This area has a population of approximately 2.5 million, 55% of the population of Zambia.

All cases of carcinoma of the bladder seen in this department during the period 1968-1972 were reviewed. As the material consisted of bladder biopsy specimens only, the size and quality varied considerably, especially as the biopsies were performed in almost all cases through the cystoscope. This determined the quality and quantity of the material available. In most cases biopsy specimens tended to be very small. It also tended to limit the geographical survey to certain hospitals with better equipment and specialist staff facilities for such diagnostic procedures. The figures presented therefore cannot be taken as a true incidence of carcinoma of the bladder in Zambia. The figures probably under-represent the actual incidence.

During the 5-year period a total of 217 cases of cancer of the bladder were collected. In all cases the original paraffin-embedded block of tissue was available for further histological examination. Routine haemotoxylin and eosin-stained sections were supplemented in selected cases with recognised special stains, where necessary.

Histological classification of the bladder tumours followed the recommended WHO classification. Diagnosis of concomitant schistosomiasis was made on the positive identification of schistosomal eggs in the sections examined.

RESULTS

Incidence
During the 5-year period carcinoma of the bladder was the third commonest cancer, which amounted to nearly 9% of all malignant tumours reported to the Southern

<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Cervix</td>
<td>138</td>
<td>12,6</td>
</tr>
<tr>
<td>Liver</td>
<td>130</td>
<td>12,4</td>
</tr>
<tr>
<td>Bladder</td>
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<td>8,3</td>
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<tr>
<td>Skin</td>
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<tr>
<td>Stomach</td>
<td>53</td>
<td>5,1</td>
</tr>
<tr>
<td>Oesophagus</td>
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<td>4,8</td>
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<tr>
<td>Lung and bronchus</td>
<td>47</td>
<td>4,7</td>
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<tr>
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<tr>
<td>Breast</td>
<td>33</td>
<td>3,2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>28</td>
<td>2,7</td>
</tr>
</tbody>
</table>

TABLE I. COMMONEST TUMOURS IN ORDER OF FREQUENCY IN ZAMBIA IN 1972 (TOTAL MALIGNANCIES REGISTERED: 1 045)
Division of the Cancer Registry of Zambia. The crude rates of the commonest malignancies encountered in Zambia during the year 1972 are given in Table I. The rates are calculated as a percentage of all malignancies seen during the year, and illustrate the position of carcinoma of the bladder in relation to other malignancies. The over-all incidence of 4.5 per 100,000 population is not unusually high when compared with figures quoted from other countries.

It seems, therefore, that the incidence of cancer of the bladder is no higher in Zambia than in countries where schistosomiasis is not endemic. The incidence is in conformity with that reported from other areas of endemic schistosomiasis.

**Age and Sex Distribution**

In the present study the age was recorded in 136 patients. Comparison of the findings in Durban Blacks in a similar study by the author shows that the age distribution in the two series is similar (Fig. 1). In this study more than 35% of the patients were 40 years old or less and nearly 60% were under 50 years.

The age distribution shows that, as is the case in other schistosomal regions, cancer of the bladder occurred in a much younger age group than that reported from non-schistosomal areas.

The male to female ratio in this study was found to be 2:1, compared to 3:1 in the Durban study. Other authors have found the male to female ratio to vary in different regions.

**Histopathology**

The histological types of carcinoma of the bladder are summarised in Table II.

**Squamous cell carcinoma:** Of the 217 cases, 75% were squamous cell cancers. The degree of differentiation varied but the majority were well-differentiated, keratinising tumours. Prominent keratin pearls were noted in the majority of cases. Some biopsy specimens consisted almost entirely of keratinised material with a few clumps of malignant cells. The gross features of such a well-differentiated tumour are illustrated in Fig. 2.

**Transitional cell carcinoma:** There were 21 cases (10%) of transitional cell cancer. These were generally well-differentiated papillary tumours (Fig. 3). Areas of squamous metaplasia were identified in some of these tumours when cystectomy specimens were available. A proper assessment of squamous metaplasia in all tumours was not possible, owing to the small specimens.
Fig. 3. A typical example of a well-differentiated papillary transitional cell carcinoma. Eggs of *S. haematobium* were identified in the base of the tumour (cystectomy specimen) (H and E x 100).

**Adenocarcinoma:** Only 7 cases (3%) of adenocarcinoma were observed. All of these tended to be well differentiated and mucous secretion was usually identified. The gross features of a widespread adenocarcinoma are illustrated in Fig. 4.

**Anaplastic tumours:** There were 26 (12%) anaplastic tumours. Some areas showed a spindle-cell, almost a sarcomatous, pattern (Fig. 5). Such tumours often bore a close resemblance to leiomyosarcomas. However, in cases where the whole tumour was available (cystectomy specimens and postmortem specimens), adequate sampling often revealed carcinomatous areas, especially in the more superficial, submucosal zones.

Fig. 4. A total cystectomy specimen which on histology proved to be a mucus-secreting adenocarcinoma. Concomitant *S. haematobium* infection was present.

Fig. 5. An example of an anaplastic carcinoma. The spindle-celled pseudosarcomatous pattern is shown. Numerous *S. haematobium* eggs are present (H and E x 100).

The histological pattern of our bladder tumours conforms to that reported from other schistosomal areas, both hyperendemic and endemic. The preponderance of squamous cell carcinoma in the present study conforms to this pattern.

The histological pattern in these schistosomal areas is unlike that reported from England and North America. Some authors have noted that squamous cell carcinoma is also the common histological variety in other tropical areas where schistosomiasis is not endemic. However, in both these regions squamous carcinoma is associated with retention, chronic cystitis and metaplasia. The possible aetiological link between chronic retention, chronic cystitis and chronic urinary schistosomiasis on the one hand and squamous carcinoma on the other, will be considered later.

**Incidence of *S. haematobium* in Bladder Cancer**

The concomitant presence of *S. haematobium* in cases of cancer of the bladder is shown in Table II. Eggs were identified in 71% of squamous cancers, but in only 52% of transitional cell cancers. An interesting feature was that eggs were identified in 86% of cases of adenocarcinoma. Collectively, eggs were identified in 65% of all cases. As the sampling from these tumours was in most cases inadequate, it is obvious that if more adequate tissue had been available, eggs would probably have been found in a greater percentage.

The incidence of schistosomiasis in Zambia is focally endemic. In this study it was found that the incidence of *S. haematobium* in endemic areas varied from 10% to 40%. An adequate survey has not yet been conducted in one area identified as hyperendemic, but from clinical and
outpatient hospital experience the incidence is obviously of a very high order, probably 80-90%.

If the hyperendemic area is excluded, the incidence of *S. haematobium* is higher in the cancer cases than in the general population, even though the biopsy specimen in most cases was unrepresentative. This pattern is consistent with that observed in other endemic schistosomal areas and in Egypt. The severity of parasitism and egg loads is more difficult to assess. By means of the digestion technique in hospital autopsies in an endemic area, the egg load in the vast majority was shown to be light. Similar studies in Lusaka, as yet incomplete, suggest a similar egg load. Incidence and egg load studies are at present also underway in Katete.

**Epidemiology of Bladder Cancer in Zambia**

Although our department serves a vast area of the country 42% of our cases came from the University Teaching Hospital (Table III). The University Teaching Hospital serves as a referral hospital and cases are referred from surrounding country hospitals. Thus, all the patients with cancer of the bladder seen at the University Teaching Hospital were not necessarily resident in Lusaka or its immediate environs. An interesting fact that emerged, however, was that 43% of our cases came from a small hospital in Katete in the Eastern Province and bordering on Mozambique. This may partly be due to the fact that special urological facilities are available in this centre, permitting bladder biopsies to be performed. However, it could be due to the greater prevalence of cancer of the bladder in this area.

<table>
<thead>
<tr>
<th>Centre</th>
<th>Number of cases</th>
<th>% of total</th>
<th>S. haematobium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lusaka</td>
<td>91</td>
<td>42</td>
<td>Endemic</td>
</tr>
<tr>
<td>Katete</td>
<td>93</td>
<td>43</td>
<td>Hyperendemic</td>
</tr>
<tr>
<td>Other</td>
<td>33</td>
<td>15</td>
<td>Endemic</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The association and possible aetiological link between schistosomiasis and carcinoma of the bladder is well known. The initial reports from Egypt, an area where *S. haematobium* infection is hyperendemic, were the first to raise this issue. The evidence for this causal relationship is the unusual pattern of bladder tumour pathology in association with urinary schistosomiasis. Egypt has been, and still is, a hyperendemic area of *S. haematobium*.

Whereas transitional cell carcinoma is the most common histological type reported from England and North America, squamous cell carcinoma is the commonest variety seen in association with schistosomiasis. Egypt has been, and still is, a hyperendemic area of *S. haematobium*.

Although the initial reports of the association of schistosomiasis and carcinoma of the bladder emanated from Egypt, workers in other African countries where schistosomiasis is endemic have noted a similar association.

The schistosomal theory of bladder cancer in endemic areas has not been universally accepted and several workers have questioned the validity of this theory on the basis that the incidence of cancer of the bladder in areas of endemic schistosomiasis outside Egypt was no higher than the expected rate. The assumption is that, since schistosomiasis is endemic in these countries and since the incidence of carcinoma of the bladder is no higher than the expected rates, schistosomiasis is not aetiologically linked to cancer of the bladder.

This simplistic approach assumes that schistosomiasis is a direct carcinogenic agent, and does not take into account the severity, the load or the duration of infection and the consequent long-term local bladder complications of urinary schistosomiasis.

The majority of authors who favour the schistosomal theory of cancer of the bladder have accepted that schistosomiasis is probably not a direct carcinogen but that it provides altered conditions and creates a milieu in the urinary bladder which is conducive to the subsequent development of cancer, i.e. it acts as a promoting agent.

**Bladder Carcinogenesis**

**Chemical carcinogens:** The direct carcinogenic effect of the aniline dyes, especially of 2-naphthylamine, one of the aromatic amines, on the bladder epithelium is well known. The metabolite 2-amino-1-naphthol is the active carcinogen but it is detoxified in the liver and excreted in the urine in the form of a glucuronide. The active carcinogenic compound, however, is again liberated in the bladder by the action of the enzyme B-glucuronidase which is normally present in bladder epithelial cells.

**Tryptophan metabolites:** Boyland *et al.* had also noted that naturally occurring aromatic amines resulted from tryptophan metabolism and were excreted in the urine in the conjugated form. They postulated that carcinogenic aromatic amines could be liberated by the action of B-glucuronidase, thus accounting for the 'spontaneous' cases of carcinoma of the bladder. Allen *et al.* demonstrated that 3-hydroxy-kynurenine and 3-hydroxy-anthranilic acid, naturally occurring aromatic amines from disordered tryptophan metabolism, were carcinogenic in laboratory animals.

Fripp meanwhile reported raised B-glucuronidase activity in urinary schistosomiasis and noted that the enzyme activity was markedly increased in active infections. This suggested that the parasite was the source of at least part of the increased enzyme content. Norden and Gelfand have confirmed the observations of Fripp, Abul-Fadl and Khalafallah also reported increased excretion of 3-hydroxy-anthranilic acid in patients with urinary schistosomiasis and cancer.

From these observations it would appear that the aetiological basis of carcinoma of the bladder in aniline dye cases, spontaneous cases and schistosomal cases may be related.

The schistosome parasites and their eggs may be providing direct chemical carcinogens, but this needs confirmation.

The possible role of other potentially carcinogenic ortho-aminophenols has also to be considered in non-schistosomal regions.
Urinary Stagnation and Bladder Cancer

There have been several reports which indicate that urinary stagnation promotes the development of urinary tract cancer. Urinary stagnation from whatever cause would allow concentration of urine-borne endogenous carcinogens and also expose the bladder epithelium to prolonged stimulation by these carcinogens.

Numerous workers, especially from Egypt, have reported on the late chronic complications of urinary schistosomiasis which commonly include bladder-neck obstruction. It is well known that S. haematobium is hyperendemic in Egypt.

Workers in endemic areas, however, have noted an absence of bladder neck obstruction. I have noted that in contrast to the severe late pathology found in Egypt, late lesions in an endemic area were the exception. The schistosomal infection was also noted to be lighter. Consequently it was postulated that the late complications, of which carcinoma of the bladder was the most serious, occurred only in those patients with heavy infections, in whom the condition would therefore be similar to that described in an hyperendemic area like Egypt. Similar findings have been noted in Zambia.

Preneoplastic Bladder Lesions Produced by Schistosomiasis

The epithelial changes associated with the chronic stage of schistosomiasis are Brunn's nests, cystitis cystica, cystitis glandularis, squamous metaplasia and leucoplakia. These metaplastic lesions are not exclusive of schistosomiasis but have frequently been described with chronic bacterial cystitis of any cause.

It has been shown that metaplasia will complicate a non-bacterial, chemical cystitis, or even cystitis due to irritation by foreign bodies in the absence of sepsis.

These changes in the bladder are not surprising in view of the known metaplastic potential of bladder epithelium. In the presence of chronic irritation, squamous metaplasia is the most frequent change noted in the bladder epithelium and, as has been discussed, squamous metaplasia is the most frequent metaplastic change associated with chronic urinary schistosomiasis.

Squamous metaplasia and leucoplakia are regarded as preneoplastic lesions. Similarly, cystitis glandularis is also regarded as preneoplastic. Some authors even regard Brunn's nests and cystitis cystica as preneoplastic lesions.

In a healthy bladder the different layers of the epithelium possess different enzymes. Metaplasia therefore not only entails a morphological alteration of tissue but also promotes a profound cytochemical and physiological aberration.

It is thus apparent that severe chronic urinary schis-