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Schistosomiasis as a Risk Factor for Bladder Cancer. Central Hospital of Nampula, Mozambique

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Abstract: Introduction: Schistosomiasis is the most important trematode infection globally. Squamous cell carcinoma constitutes 2% of all the histological types of bladder cancer; however, the incidence of this variety of cancer in squistosomiasis-endemic countries is higher. Objective: To evaluate the relationship between squistosomiasis and bladder cancer in patients from the Central Hospital of Nampula. Materials and methods: A cross-sectional descriptive observational study was carried in the period between January 2014 and December 2020. Patients were divided into age-groups, by 10-year intervals. Biopsy samples of bladder tumors were taken, classified by histological type, in addition to findings related to squistosomiasis infestations and bladder cancer presentation forms. The universe consisted of 184 patients and the sample of 135 cases. Results: it was found that the largest number of patients with bladder cancer is male; squamous cell carcinoma is the most frequent histological type, representing 84.3% of the total. Cystitis, schistosome and their eggs were present in almost all the biopsies performed. Its most frequent presentation forms were hematuric and painful cystitis. Conclusions: Bladder cancer showed higher incidence at the ages between 30 and 69 years. The squamous cell carcinoma was the most frequent, and its relationship with cystitis and schistosome infection was present in more than 90% of biopsies.

Key words: bladder cancer; schistosomiasis; cystitis; hematuria

1. Introduction

Schistosomiasis is by far the most important trematode infection. Schistosoma is the only trematode that invades the skin; all others only infect the body orally. There are about 221 million infected people worldwide. [1]

It is very common in rural and impoverished populations. The main risk factor for infection is exposure to fresh water contaminated with parasite-infected human feces, through domestic, occupational or recreational activities. Diagnosis requires the identification of eggs in feces, urine or a biopsy specimen. Serological tests can be sensitive and specific, but do not provide information on helminth load or clinical status. [1, 2, 3]

Five species of schistosomes infect humans and all have similar life cycles related to the freshwater snail.

S. haematobium causes urinary tract infection, and other species of schistosomes cause intestinal disease.

The number of deaths attributable to schistosomiasis is difficult to estimate due to the existence of hidden related pathologies such as liver and kidney failure and bladder cancer. It is estimated that at least 92% of people in need of treatment for schistosomiasis live in Africa. The World Health Organization [2] identified it as the second most important human parasitic disease in the world after malaria.

Mature schistosome infections are associated with a local, chronic inflammatory response to schistosome eggs trapped in host tissues, which can lead to inflammation and obstruction of the urinary tract (S. haematobium) or to intestinal disease, hepatosplenic inflammation and liver fibrosis (S. mansoni, S. intercalatum, S. japonicum, S. mekongi).

Urinary tract disease develops after infection with S. haematobium, and granulomatous inflammation is the response to egg deposition in the urinary tract tissues (bladder and ureter). [1] Hematuria appears 10 to 12 weeks after infection and is the first sign of established disease. Dysuria and hematuria occur both early and in the late stages of the disease. The final manifestations of the disease are proteinuria (often as nephrotic syndrome), bladder calcification, urethral obstruction, secondary bacterial urinary tract infection, renal colic, hydronephrosis and renal failure. Structural abnormalities of the urinary tract may be present in children. [3]

S. haematobium-associated squamous cell carcinoma of the bladder tends to be well differentiated and to give local metastases. S. haematobium causes genital disease in approximately one-third of infected women.

In Mozambique, the first case of urinary schistosomiasis was reported in Nampula in 1904 as "tropical hematuria." [3, 4, 5] However, the first national survey on schistosomiasis was not conducted until 1952-1957 by the Institute of Tropical Medicine in Lisbon. In 1993, Gama Vaz [6] observed that 7.5% of patients with urinary schistosomiasis in Mozambique develop bladder carcinoma, and 59% of them develop squamous cell carcinoma. [7]

Schistosoma can inhabit a human organism for a period of 20 to 30 years, with an average survival that varies from 5 to 10 years. During this period, it cyclically lays eggs, some of which are eliminated in the urine and others adhere to the bladder mucosa causing calcifications, even causing instability of detrusor motility, which explains systems present in this disease. A concentration of 260,000 to 710,000 eggs per cm^2 of bladder area will correspond to bladder calcifications, which may be the radiological translation of retractile bladders called "porcelain bladders". [8]

The deposition of eggs in the bladder mucosa causes local lesions with hyperemia and results in granulomatous reactions that progress to fibrosis, leading to chronic cystitis. Initially, the mucosa forms yellowish subepithelial nodules that concentrate at the level of the bladder trigone, leading to hyperplasia, fibrosis and muscular hypertrophy, which progress to polypoid lesions. [8]

Urinary stone formation occurs as a consequence of superficial changes in the bladder mucosa along with egg deposits. Other complications resulting from the host response, such as chronic inflammation, range from metaplasia to the development of bladder cancer. [4, 8, 9]

In most cases, the presence of blood in the urine is the first sign of bladder cancer. There may be enough blood to change the color of the urine to orange, pink, or less frequently to darker red. Hematuria is the cardinal sign of bladder cancer and is generally asymptomatic. The risk of urothelial cancer is proportional to the amount of hematuria. [10]

There may be blood in the urine one day and no blood the next day, and the urine may remain bloodless for a few weeks or even months. But at some point the blood reappears. [11]

Bladder cancer (BC), the most frequent malignant tumor of the urinary tract, is the fourth most common cancer in men. This tumor is most common in those over 50 years of age (80%) and accounts for 6% of all male cancers and 2% of female cancers; patients often suffer multiple lesions, and in many patients these tend to recur. [9] In addition, incidence

rates in white men are twice as high as in black men. Almost all malignant bladder neoplasms involve the lateral and posterior bladder walls and trigone. Patients frequently suffer multiple lesions, and in many patients these tend to recur repeatedly. Thus, a high percentage of patients experience several, usually non-lethal, tumor episodes, sometimes remaining disease-free for years. Locally advanced invasive disease, and disseminated disease, show dismal survival rates, despite all therapeutic efforts. [8, 9]

In the United States, there are an estimated 50,000 new cases per year, with more than 10,000 deaths per year. In Spain, it has been estimated that approximately 20 out of every 100,000 inhabitants over 50 years of age develop bladder carcinoma, and that the mortality trend is almost 10% for men and just over 2% for women. [12, 13]

A study conducted by the European Association of Urology in 2018, on a review and update of BC epidemiology, [7] posited that about 430,000 new cases of BC occurred worldwide and 165,000 deaths from this disease. The main related risk factor was tobacco use, and the second was exposure to certain carcinogens in the workplace and in the environment. Seventy-five percent of the patients diagnosed had non-musculo-invasive disease confined to the mucosa and submucosa.

Urothelial cell carcinoma, also known as transitional cell carcinoma, is the most common type of bladder cancer. Squamous cell carcinoma accounts for 1-2% of bladder tumors. In general, almost all are muscle-invasive, and the light microscope shows cells very similar to the flat epithelium of the skin; however, in countries where schistosomiasis is endemic, squamous cell carcinoma is the most frequent histologic type, exceeding 70% of BCs (mainly in Africa and the Middle East). [14, 15, 16]

Only about 1% of bladder cancers are adenocarcinomas. These cancer cells have much in common with the gland-forming cells of colon cancers.

Sarcomas originate in the muscle cells of the bladder, although they are very rare in the bladder. Small cell carcinoma begins in neuroendocrine cells that have characteristics of nerve cells. These cancers often grow rapidly and usually need treatment with chemotherapy, such as that used for small cell carcinoma of the lung. [13-15]

According to data obtained by the World Cancer Observatory, [17] in 2020 in Mozambique bladder cancer ranked eighth, with an incidence of 3.5%, showing, in addition, rates of 2.9% of cancer deaths. In Nampula, we noted a high incidence of schistosomiasis in patients with bladder cancer, which prompted a study on schistosomiasis as a risk factor for BC.

2. Materials and Methods

An observational, descriptive, cross-sectional study was conducted in the period from January 2014 to December 2020.

The biopsies of the patients studied, histological type, biopsy findings, as well as the clinical symptoms taken from the clinical histories were taken. The universe consisted of 184 patients, and the sample consisted of 135 cases diagnosed with bladder cancer. Formal approval for the study was requested through the Teaching Department. The investigators reviewed the medical records and examinations performed on the patients studied, which were on file at the hospital.

The variables used were: sex, age, histologic type, associated histologic findings, and forms of presentation of the disease. The instrument used to obtain the information was a data collection form.

The identities of the patients and the confidentiality of the information obtained were protected in the present study, in accordance with the ethical principles for medical research involving human subjects, established in the Declaration of Helsinki, as amended at the 52nd General Assembly of the World Medical Association, held in Edinburgh, Scotland, in October 2000.

3. Results

It is observed that more than 60% of the patients are male, with the occurrence of BC being more frequent in the 40 to 69 age groups (Table 1).

Table 1. Distribution of patients according to age group and sex at the Nampula Central Hospital

Ages	Male		Female		Total	%
	Total	%	Total	%		
0 - 9	1	0.5	-	-	1	0.5
10 - 19	3	1.6	2	1.1	5	2.7
20 - 29	6	3.3	3	1.6	9	4.9
30 - 39	13	7.1	9	4.9	22	12.0
40 - 49	28	15.2	15	8.2	43	23.4
50 - 59	21	11.4	8	4.3	29	15.8
60 - 69	24	13.0	13	7.1	37	20.1
70 - 79	15	8.2	7	3.8	22	12.0
80 - 89	6	3.3	3	1.6	9	4.9
90 and over	5	2.7	2	1.1	7	3.8
Total	122	66.3	62	33.7	184	100

The most frequent histological type in the biopsies performed was squamous cell carcinoma, with a total of 113 patients, representing 61.4 %, followed by urothelial cell carcinoma and rhabdomyosarcoma respectively; but the number of these is significantly lower (Table 2).

Table 2. Distribution of patients with bladder cancer according to histologic type

Ages	Histological types										Total	%
	SCC		UCC		RMS		ADC		Others			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0 - 9	-	-	-	-	-	-	-	-	1	33.3	1	0.7
10 - 19	-	-	1	9.1	-	-	-	-	1	33.3	2	1.5
20 - 29	3	2.7	-	-	-	-	-	-	-	-	3	2.2
30 - 39	13	11.5	2	18.2	-	-	2	66.7	-	-	17	12.6
40 - 49	28	24.8	4	36.4	2	40	-	-	-	-	34	25.2
50 - 59	23	20.4	2	18.2	1	20	-	-	-	-	26	19.3
60 - 69	27	23.9	1	9.1	1	20	-	-	-	-	29	21.5
70 - 79	14	12.4	1	9.1	1	20	-	-	1	33.3	17	12.6
80 - 89	3	2.7	-	-	-	-	-	-	-	-	3	2.2
90 and over	2	1.8	-	-	-	-	1	33.3	-	-	3	2.2
Total	113	100	11	100	5	100	3	100	3	100	135	100

SCC: squamous cell carcinoma; UCC: urothelial cell carcinoma; RMS: rhabdomyosarcoma; ADC: adenocarcinoma of the bladder; others: other histological types.

Cystitis, a product of the same parasitic invasion of the eggs and the lesions they cause in the urothelium, is present in more than 90% of SCC, being the most frequent anatomopathological finding (Table 3).

Table 3. Pathologic findings associated with bladder tumor

T. histol type	Cystitis		P. schistosom		P. eggs		Cel eosinof.		Queratosis		Necrosis	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
SCC	105	92.9	105	92.9	61	54	19	16.8	31	27.4	16	14.2
UCC	10	90.9	2	18.2	1	9.1	-	-	1	9.1	-	-
RMS	5	100	2	40	-	-	1	20	-	-	1	20
ADC	2	66.7	1	33.3	1	33.3	-	-	-	-	1	33.3
Others	1	33.3	1	33.3	1	33.3	1	33.3	-	-	1	33.3

T. histol: histological type; P. schistosom: positive for schistosomiasis: P. eggs: positive for eggs.

In this study, hematuria and cystitis were present in 72.6 % of the patients; the painful or dysuric form was present in 47.4 % of the sample studied.

The presence of associated urinary tract infections was present in 42.2 % of the histories reviewed, predominantly E. coli and Citrobacter. The presentation of palpable tumor (40.7 %) was the predominant one (Table 4).

Table 4. Forms of presentation of bladder cancer according to histological type

Presentation	Tumor types										Total	
	SCC		UCC		RMS		ADC		Others			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematuria	91	92.9	3	3.1	2	2	1	1	2	2	98	72.6
Cystitis	93	94.9	2	2	1	1	1	1	1	1	98	72.6
Painful	60	93.8	-	-	1	1.6	2	3.1	1	1.6	64	47.4
Infectious	46	80.7	2	3.5	2	3.5	-	-	-	-	13	42.2
Tumor	46	83.6	2	3.6	1	1.8	2	7.7	-	-	26	40.7
Metastatic	16	80	2	10	-	-	2	10	-	-	20	14.8
Other	3	75	-	-	-	-	1	25	-	-	4	3

4. Discussion

BC is a disease that can be diagnosed at any age, although it is rarely diagnosed before the age of 35 and most cases are reported after the age of 60. However, in this study, the data obtained differ from the above. The appearance of BC has been attributed to risk factors and the time of action of these factors involved in carcinogenesis, especially those related to inflammation and chronic infection by schistosomiasis. This study shows that the greatest number of patients diagnosed with BC are between 30-69 years of age, which together represent 71.3% of the total. The incidence after 70 years of age is also lower than those published by other authors, which could be related to the life expectancy of the Mozambican population.

The male/female ratio is 2:1; however, this ratio differs from that of other authors, which is related to the impoverishment of the population, the impossibility of access to drinking water and, consequently, to the contamination of water sources. It is also related to the culture of these countries, where many activities of daily life are carried out using water from rivers and ponds, mostly with the presence of schistosome cercariae. [2]

More than 90% of bladder cancers correspond to transitional cell carcinomas, which by international consensus are called urothelial cancers, thus differentiating them from other histological types, such as squamous cell carcinomas or adenocarcinomas (but which also originate in the urothelium).

In the United States, only about 1 to 2% of bladder cancers are squamous cell carcinomas. It should be noted that almost all squamous cell carcinomas of the bladder are invasive.

Only about 1% of bladder cancers are adenocarcinomas. These cancer cells have much in common with the gland-forming cells of colon cancers. Almost all adenocarcinomas of the bladder are invasive.

Squamous cell carcinoma is a primary neoplasm of urothelial origin containing keratinized islet cells. It accounts for approximately 5% of primary bladder tumors in the West, while in countries such as Egypt, where schistosomiasis is endemic, it may account for up to 75% of cases. [7, 9, 15]

If we compare our study with the above, we appreciate that our results are much higher; there is also a substantial difference with those reported by Adeloye et al. [16].

Among the main anatomopathological features found, inflammatory lesions were present in almost all biopsies. In addition to the presence of the parasite and its eggs, eosinophilia was another frequent finding, due to parasite invasion and host response. Keratosis and necrosis were other findings, and all of these, in turn, predominated in SCC. [3, 11, 12] According to various theories, schistosome eggs may release prooncogenic substances such as tryptophan metabolites, N-nitroso compounds and beta-glucuronidase, favoring tumor development. [3]

Schistosomiasis can cause hemorrhagic cystitis, especially those produced by S. haematobium, where ulcers in the bladder wall can cause dysuria, hematuria and pollakiuria. Chronic cystitis develops over time. Strictures can lead to hydroureter and hydronephrosis. Blood loss through the urogenital and digestive tract often results in anemia. [3, 16] All of them demonstrated in our work.

In particular, S. haematobium can cause genital disease in both females and males, leading to numerous complications, including sterility.

It is noteworthy that 40.7% of the patients studied had palpable tumor masses in the hypogastrium in their medical records, suggesting advanced stages of the disease.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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