

The Impact of Schistosomiasis on the Pathology of Bladder Carcinoma

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In a series of 1095 Egyptian patients with carcinoma of the bladder treated by radical cystectomy, 902 cases (82.4%) contained schistosome eggs in the specimens, and 193 (17.6%) were egg-negative. The different tumor parameters were compared in these subgroups to explore any differences that could be related to schistosomal infestation. In egg-positive cases, the tumors developed at a younger age (46.7 years) than in egg-negative cases (53.2 years). Squamous cell carcinoma, commonly of low grade, predominated in the egg-positive group. No difference was observed in the frequency of tumor stages or lymph node metastases between the two subgroups. The limited tendency to distant spread in schistosomal bladder cancer, despite its advanced local stage, is accounted for by the high frequency of low grade tumors rather than the limiting effect of local schistosomal tissue reactions.

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CARCINOMA OF THE URINARY BLADDER is the foremost oncologic problem in Egypt.^{10,12} It also occurs in high frequency in other parts of Africa^{3,4,17,19} and the Middle East.^{27,28} Because of the geographic coincidence of bladder cancer and endemic bilharziasis, a causal relation has long been speculated to exist between them.¹³ This association determines a distinct clinicopathologic entity,^{9,22} quite different from that experienced in the Western world.^{2,23} In the first place, the tumor is found mostly in a relatively young age group.⁷ It is commonly a well-differentiated squamous cell carcinoma^{7,20} with a limited tendency to lymphatic and blood stream spread,^{9,14} despite the locally advanced stage of tumors in the majority of patients.¹⁵ Tissue reactions to schistosome eggs in the bladder wall, pelvic lymphatics, and regional lymph nodes were proposed as limiting factors against neoplastic spread.^{5,9} The tumors are multiple in 22% of cases and are frequently associated with atypical epithelial changes in the rest of urothelium.²¹ Accordingly, radical cystectomy is the treatment of choice.^{9,14}

In Egyptian cases, it is common to find *Schistosoma haematobium* eggs in association with the carcinoma, either in the bladder wall or in the seminal vesicle. However, cases are also recognized in which schisto-

some eggs are absent even after careful study of the cystectomy specimens. The presence of these two groups of patients offers a good opportunity for comparative studies to evaluate the impact of schistosome eggs in the bladder on the pathologic features of the carcinoma. The present study explores this problem in a large series of Egyptian patients with bladder cancer.

Material and Methods

The study was based on 1095 patients with bladder carcinoma, all treated by radical cystectomy. The material was compiled during the three-year period 1976-1978 from three sources: the National Cancer Institute, Cairo, Egypt, the Department of Urology, Mansura University, and the private practice of the first author. The contribution of the Cancer Institute included 732 cases, of which 88.7% showed calcified schistosome eggs in the specimens. A total of 86 cases were obtained from the Department of Urology, Mansura, of which 89.5% were egg-positive. Conversely, in private cases, a lower frequency of schistosome eggs was observed in the specimens. Thus, 63.5% of the 277 cases obtained from private practice was egg-positive.

All cystectomy specimens were examined by the same pathologic protocol. Tissue sections were obtained from the tumor, the bladder wall both near and remote from the tumor, the ureters, and the regional lymph nodes. In males, tissues were also studied from the seminal vesicle and prostate including the urethra. In females, tissues were also obtained for study from the ovaries and uterus. Pathologic staging of the tumors was done

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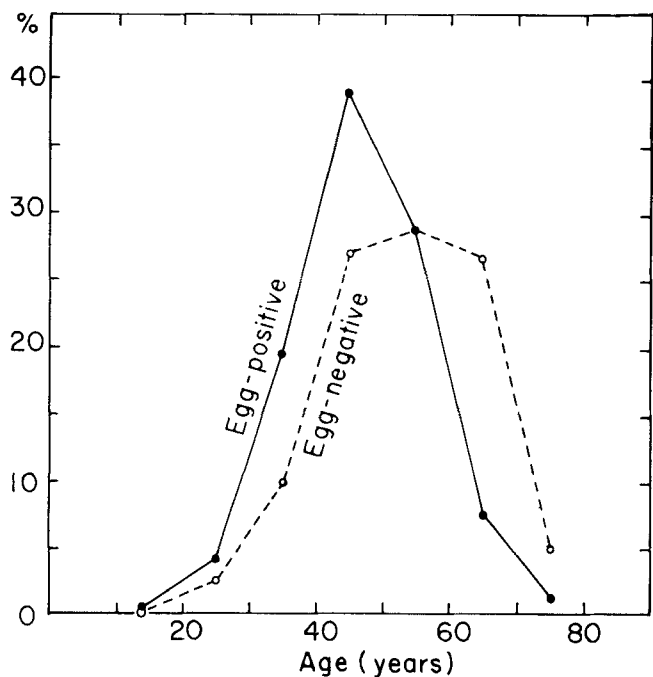


FIG. 1. Age distribution relative to schistosome eggs in the specimens.

according to the TNM classification of UICC.^{18,15} In this system, the tumors were classified into carcinoma *in situ* (PIS), invasion of lamina propria only (P1), superficial invasion of muscle not exceeding its middle

(P2), deep muscle invasion or perivesical spread (P3), and extra vesical spread (P4).

For histopathologic typing and grading of tumors, the WHO classification²⁵ was adopted slightly modified to include the verrucous variant of squamous carcinoma unique to the schistosomal series.^{7,11} According to this system, the tumors are typed according to cellular differentiation and divided into three grades based upon the degree of anaplasia. Carcinoma *in situ* is used to describe epithelial lesions with features of malignancy but without infiltration of the lamina propria. In the present series, only two cases of carcinoma *in situ* treated by radical cystectomy were encountered, one of them a low grade squamous type and the other a high grade transitional type. Squamous carcinoma exhibits squamous differentiation throughout the whole lesion. Two subtypes are recognized: the invasive variety and the verrucous variety. The latter is a hyperkeratotic low grade tumor with elongated surface projections. The deep advancing margin has a pushing rather than an infiltrating border, where the cells are arranged in large bulbous masses of tightly cohesive cells lacking anaplastic features. Transitional carcinomas include papillary tumors of more than six layers thick and the frankly invasive transitional tumors. These transitional carcinomas are frequently seen as a pure form of one cell type. However, transitional carcinomas with tumor metaplasia are also observed. This term describes the presence of foci of squamous or glandular differentia-

TABLE 1. Histopathologic Types and Grades of Bladder Carcinomas

	Schistosome eggs	Grade (%)			Total	
		1	2	3	No.	%
Squamous	Positive	41.5	36.8	21.7	691	76.6
	Negative	31.8	33.6	34.6	107	55.4
	Total	40.2	36.3	23.4	798	72.9
Verrucous	Positive	87.5	12.5	0.0	32	3.5
	Negative	100.0	0.0	0.0	1	0.5
	Total	87.9	12.1	0.0	33	3.0
Transitional	Positive	2.9	40.8	56.3	103	11.4
	Negative	15.6	40.0	44.4	45	23.3
	Total	6.8	40.5	52.7	148	13.5
Transitional with metaplasia	Positive	11.1	55.6	33.3	18	2.0
	Negative	11.1	33.3	55.6	9	4.7
	Total	11.1	48.1	40.7	27	2.5
Adenocarcinoma	Positive	31.7	29.3	39.0	41	4.5
	Negative	21.7	52.2	26.1	23	11.9
	Total	28.1	37.5	34.4	64	5.8
Undifferentiated	Positive	0.0	0.0	100.0	17	1.9
	Negative	0.0	0.0	100.0	8	4.1
	Total	0.0	0.0	100.0	25	2.3
TOTAL	Positive	37.0	35.7	27.3	902	100
	Negative	24.9	35.8	39.3	193	100
	Total	34.8	35.7	29.5	1095	100

tion in a predominantly transitional neoplasm. Adenocarcinoma includes glandular, tubular, or mucinous varieties. Undifferentiated carcinoma describes tumors that cannot be classified or typed into any of the above mentioned categories.

Precoded forms were used to register the data which included patient's identification, age and sex, different pathologic parameters of the tumor and finally information on the presence or absence of schistosome eggs in the specimen. These data were transferred to punch cards and fed into a computer. In the final analysis, the material was separated into two groups according to the presence or absence of schistosome eggs in the cystectomy specimens. These groups will be referred to in this text as egg-positive and egg-negative cases respectively. The data of these groups were compared by standard statistical methods, namely the *t* test for evaluating difference in the age incidence and test of proportion for all the other statistical analyses.

Results

The mean age in years for the total series was (48.3 ± 10.9). It was higher in the egg-negative cases (53.2 ± 11.6) than the egg-positive cases (46.7 ± 10.1). The difference was statistically significant (*t* test, *P* < 0.001). The earlier age peak for the egg-positive patients is presented in Figure 1. Of the total series, 923 were men, a sex ratio of 5.4:1. The sex ratio was higher in egg-positive cases (5.6:1) than the egg-negative cases (4.3:1); however, this difference was statistically insignificant.

A difference in the distribution of tumor types and grades was observed among the egg-positive and egg-negative groups (Table 1). Although the ranking of the different tumor types was the same in both groups, the frequency of individual tumor types was significantly different. Thus, squamous cell carcinoma was more frequent in egg-positive cases, whereas, transitional cell carcinoma and adenocarcinoma were more frequent in the egg-negative group. The distribution of tumor grades also varied between the two groups. Thus, in egg-positive cases, well-differentiated (grade 1) carcinomas predominated, whereas in egg-negative group, poorly differentiated (grade 3) tumors were more fre-

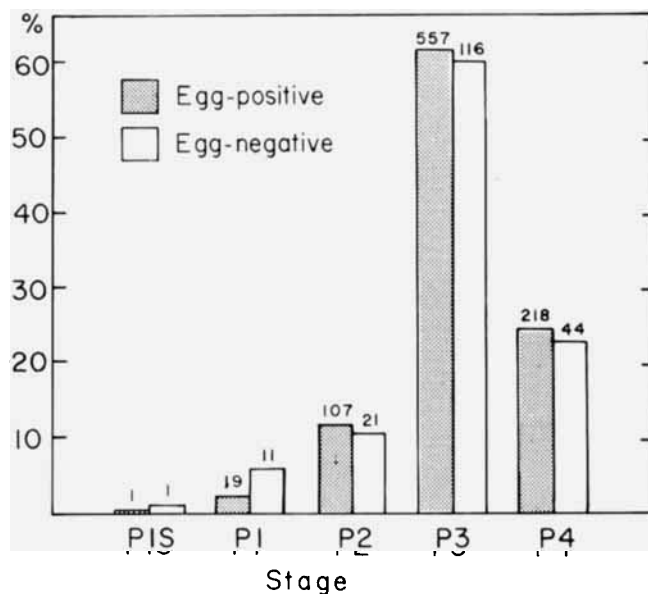


FIG. 2. Pathologic stages of the tumors relative to schistosome eggs in the cystectomy specimens.

quent. No correlation was obtained between the different grades and stages of the tumors (Table 2).

The association of schistosome eggs with the tumor had no significant effect on its pathologic stage or lymph node spread. The distribution of the pathologic stages in the egg-positive and egg-negative cases was not significantly different (Fig. 2). There was no difference in the frequency of lymph node metastases between the two groups; even within subgroups of the same tumor type and grade (Tables 3 and 4). However, lymph node metastases varied with tumor type, being least frequent with squamous cell carcinoma (Table 3). Also, lymph node metastases increased with the increase in tumor grade (Table 4).

Discussion

The distinctive clinicopathologic features of schistosomal bladder cancer was emphasized by various Egyptian investigators.^{7,9,12,21} In these reports, since most of the patients came from rural areas, the term "bilharzial bladder cancer" was generally applied to describe these

TABLE 2. Correlation of Grade and Stage of Carcinoma of the Bladder

	PIS		P1		P2		P3		P4		Total
	No	%	No	%	No	%	No	%	No	%	
Grade I	1	0.3	21	5.8	52	14.3	206	56.7	83	22.9	363
Grade II	0	0.00	8	2.00	58	14.5	245	61.4	88	22.1	399
Grade III	1	0.30	1	0.30	18	5.4	222	66.7	91	27.3	333
TOTAL	2	0.2	30	2.7	128	11.7	673	61.5	262	23.9	1095

TABLE 3. Lymph Node Metastasis in Different Histologic Types

	Eggs positive			Eggs negative		
	Total no.	Positive nodes		Total no.	Positive nodes	
		No.	%		No.	%
Squamous	691	107	15.5	107	21	19.6
Verrucous	32	0	0.0	1	0	0.0
Transitional	103	26	25.2	45	7	15.6
Transitional with metaplasia	18	9	50.0	9	5	55.6
Adenocarcinoma	41	11	26.8	23	7	30.4
Undifferentiated	17	6	35.3	8	2	25.0
TOTAL	902	159	17.6	193	42	21.8

series, but no attempt was made to classify the patients by documented evidence of schistosomiasis. An accurate classification on this basis can only be achieved by careful study of radical cystectomy specimens for schistosome eggs. This approach was followed in the present study, and the different tumor factors were compared in the egg positive and egg-negative specimens. Of the total 1095 total cystectomy specimens, 902 (82.4%) contained calcified *Schistosoma haematobium* eggs. Such egg-positive cases were often observed in peasants who suffer the most severe and repeated schistosomal infestation. Egg-negative specimens contributed only 193 cases (17.6%). These represented either nonbilharzial patients from urban areas or patients with mild bilharzial infestation who had been successfully treated and cured. It is rather difficult to separate these two subgroups of the egg-negative patients due to the present lack of a laboratory method to identify those who are cured of previous bilharzial infestation. Moreover, information on past history is liable to some bias, since bilharzial patients from rural areas may give a false negative history because of fear of receiving the anti-bilharzial injections.

Bladder carcinoma was encountered at an earlier age (46.7 years) in patients with schistosome eggs in the specimens than those of egg-negative cases (53.2 years). This observation supports the important role played by schistosomal infestation and/or associated complications in bladder carcinogenesis. The age peak for egg-positive cases was a sharp one at the age of 45 years. However, in egg-negative patients, the age distribution showed a plateau between the ages of 40 years to 70 years with a vague peak at the age 55, one decade later than the previous group. This plateau suggests that egg-negative patients possibly represent a heterogeneous group, namely a younger subgroup of rural population with mild schistosomiasis that was successfully treated and cured and a second subgroup of true nonbilharzial

patients from urban areas who usually have bladder cancer at a later age.

The possible role played by schistosome eggs in bladder carcinogenesis is poorly understood. Makar²² suspected a carcinogenic toxin produced by the miracidium, but this hypothesis was not confirmed by recent studies.¹ Mechanical irritation of the urothelium was originally proposed by Ferguson¹³ to explain malignant transformation. This was recently supported by experimental data on schistosome-infested mice treated by carcinogens, which demonstrated the importance of local irritation of bladder. Chronic bacterial infection, commonly complicating urinary schistosomiasis, is probably an important etiologic factor. Recent studies have implicated urinary tract bacteria in the production of nitrosamines, well known potent carcinogens, from their precursors in urine.⁸ Finally, injury to the urothelium by the passing eggs and/or bacterial infection might decrease the effectiveness of the mucosal barrier to reabsorb carcinogens in urine.

Squamous cell carcinoma, including its verrucous variant, constituted 75.9% of the total present series. This agrees with the high frequency of this tumor type in other recent reports from Egypt, which varied between 66.7% to 76.7%.^{7,21} It contrasts sharply with the relative infrequency of true squamous cell carcinoma in the Western world, which varies between 1.6%²⁶ and 7%.²⁴ In the present series, the frequency of squamous cell carcinoma was significantly higher in the egg-positive cases (76.6%) than in the egg-negative cases (55.4%). The frequency of low grade tumors (Grade 1 and 2) was higher in the former group. Verrucous squamous carcinoma also showed a striking predominance in the egg-positive patients. This rare variant of squamous carcinoma, which has only been reported to occur in the schistosomal bladder,¹¹ is characterized by a low grade malignancy and absence of lymph node or distant spread. The predominance of squamous cell carcinoma

TABLE 4. Lymph Node Metastasis in Different Tumor Grades

	Eggs positive			Eggs negative		
	Total no.	Positive nodes		Total no.	Positive nodes	
		No.	%		No.	%
Grade 1	333	29	8.7	48	5	10.4
Grade 2	322	54	16.8	69	12	17.4
Grade 3	247	76	30.8	76	25	32.9
TOTAL	902	159	17.6	193	42	21.8

in schistosomal series is related to squamous metaplasia of the urothelium, which is relatively common in chronic bilharzial cystitis and frequently associated with the carcinoma.²¹ However, in the present study, the frequency of squamous cell carcinoma in the egg-negative cases was still higher than that reported in the Western literature. This finding should draw the attention to other environmental or nutritional factors, such as a possible vitamin A deficiency in these patients.

Fibrosis of the bladder wall of schistosomal origin has long been suspected as a limiting factor against tumor spread.⁹ Recently, Eissa and associates⁵ correlated tumor spread with the bilharzial pathology in 60 cystectomy specimens, of which 51 were associated with schistosome eggs. In the bilharzial cases, they described a lower tendency of local spread and lymph node metastases. This was explained by fibrosis in the bladder wall and reactive hyperplasia in the regional lymph nodes. Different results were obtained in our studies, since in egg-positive cases, the frequency of different tumor stages and lymph node metastases was the same as in egg-negative cases.

In spite of the advanced local stage of bladder cancer in Egyptian patients, the frequency of lymph node metastases is rather limited and generally comparable to those reported from Western countries. In the present series, 935 cases (85.4%) were advanced tumors (stages P3 and P4), and lymph node metastases were recorded in 18.4% of cases. A very close figure of lymph node metastases of 19% was reported by Whitmore and associates³⁰ in a series of 136 patients with a lower frequency (61.8%) of advanced tumors. This limited tendency of lymphatic spread of advanced tumors in schistosomal patients is mainly explained by the predominance of low grade tumors in these patients.

In our series, only 29.5% were poorly differentiated (Grade 3), compared with a figure of 49.3% in the series of Whitmore and associates.³⁰ Thus in schistosomal series, the unfavorable effect on prognosis of advanced local tumor stage is counterbalanced by a higher frequency of low grade tumors. For this reason, the end

results of treatment of schistosomal series are closely similar to those reported from Western countries. In a bilharzial series of 1007 patients subjected to radical cystectomy and reported by El-Sebai,¹² the overall five-year survival was 27.3%. In another series of 162 patients reported in 1976 by Ghoneim and associates,¹⁶ the actuarial five-year survival was 38.9%. These figures are comparable to the survival data of bladder cancer experienced in the United States. Thus, in a series of 230 patients reported in 1962 by Whitmore and Marshall,²⁹ the five-year survival following radical cystectomy was 21%. In a recent series of 136 patients treated by Whitmore and associates,³⁰ the five-year survival rate was 33.1%.

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