CARCINOMA OF THE BILHARZIAL URINARY BLADDER

A Study of the Associated Mucosal Lesions in 86 Cases

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The mucosal lesions in the lower urinary tract were examined in 86 cystectomy specimens of bilharzial bladder cancer. Squamous cell carcinoma occurred in 66 cases, transitional cell carcinoma in 18 cases, and adenocarcinoma in two cases. Multiple infiltrative carcinomas were found in 19 cases (22.1%), and these were commonly of the transitional cell type (63.9%). Squamous metaplasia was found in 65.1%, columnar metaplasia in 52.3%, and carcinoma in situ in 40.7%. The ureters, trigone, and urethra were rarely affected by these lesions. Carcinoma in situ was more commonly associated with multiple carcinomas (68.4%) than with single tumors (32.8%). Squamous metaplasia was found in 81.8% of squamous cell carcinomas and in 16.7% of transitional cell carcinomas. The two cases of adenocarcinoma were associated with columnar metaplasia in the adjacent mucosa. Squamous cell carcinoma and adenocarcinoma probably arise from metaplastic epithelium. Total or subtotal cystectomy is recommended because of the high incidence of carcinoma in situ (40.7%) and multiple carcinomas (22.1%).

CARCINOMA OF THE URINARY BLADDER IN Egypt is usually preceded by bilharzial infestation. It differs from nonbilharzial bladder cancer by the predominance of squamous cell carcinoma, by the frequent association of metaplastic and proliferative lesions, and by the relative rarity of the trigone as a site of origin.[2,4,6] A study of these mucosal lesions, which is the aim of the present report, may help to clarify the evolution as well as the distinctive clinicopathologic features of this carcinoma.

MATERIALS AND METHODS

Eighty-six patients with carcinoma of the urinary bladder treated by radical cystectomy were studied. Their ages ranged from 20 to 64 years, and 73 (84.8%) of them were men. The bladder specimens were opened by reflecting anterior and superior flaps, as shown in Fig. 1. This method facilitated the identification of the different surfaces of the bladder and hence the localization of the lesions. Tissue sections were taken from the carcinoma, and mucosal lesions from different surfaces of the bladder, prostatic urethra, and ureters. In case of multiple carcinomas, tissues were taken from the mucosa intervening between the tumors to exclude any submucosal spread. Sections were stained with hematoxylin and eosin. In case of carcinoma in situ, Wilder's reticulum stain was done to exclude any infiltration of the stroma.

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RESULTS

Pathologic features: The majority of the carcinomas were at an advanced stage and measured 5–10 cm in largest diameter. Grossly, 70 cases (81.4%) appeared as a nodular fungating mass. The carcinoma was diffusely infiltrative in eight cases (9.3%), ulcerative in five cases (5.8%), papillary in two cases (2.3%), and, in one case (1.2%), the carcinoma appeared as a keratinized fibrillary lesion. The common sites of origin of carcinoma were the lateral surfaces, posterior, and vault (Table 1). The trigone was a relatively rare site (2.3%).

Multiple carcinomas were found in 19 out of the 86 specimens studied, an incidence of

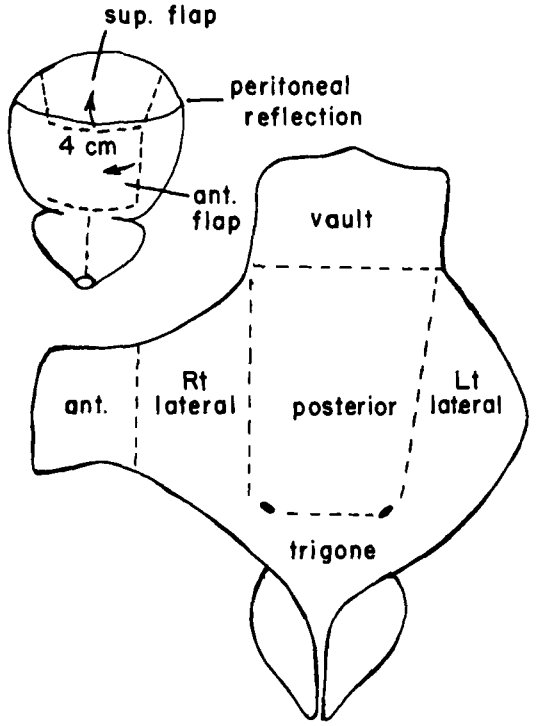

FIG. 1. *Opening the bladder specimen by making anterior and superior flaps. The landmarks of the six surfaces of the opened bladder are shown.*

22.1%. In six cases, the diagnosis of multiplicity was missed clinically and also by gross examination; this was detected only after histologic examination of the specimens. The multiple carcinomas in these cases were of rather small size (1–2 mm). False-positive diagnosis of multiplicity was also made on four occasions. These cases were diagnosed as carcinoma on cystoscopic and gross examination, but proved to be bilharzial granulomas on histologic study. Multiple tumors were of different size and usually appeared as a large main tumor associated with smaller ones. Except for one case, the tumors were widely separated and involved different surfaces of the bladder (Fig. 2). The number of carcinomas detected in each specimen was as follows: seven cases had two tumors, eight cases had three or four tumors, and four patients had more than four tumors. The maximal number of carcinomas detected in a single case was 12, and all these were of the transitional cell type. The total number of carcinomas detected in these 19 cases was 72.

The various histologic types and grades of carcinoma are presented in Table 2. Squamous cell carcinoma was the most common type (76.7%), and it was well differentiated in

TABLE 1. Site of Carcinoma of the Bilharzial Bladder in 86 Cystectomy Specimens

Site	No.	Per cent
Right lateral	22	25.6
Posterior	19	22.1
Left lateral	17	19.8
Vault	16	18.6
Anterior	10	11.6
Trigone	2	2.3
TOTAL	86	

45.5% with abundant keratinization. Transitional cell carcinoma was found in 20.9%, and it was poorly differentiated in 61.1% of the cases. Adenocarcinoma was found in two of the 86 specimens examined.

All the multiple carcinomas studied were infiltrative, and the intervening tissue between the tumors did not show evidence of submucosal spread. The incidence of histologic types in multiple and single carcinomas is compared in Table 3. Multiple tumors (63.9%) were commonly transitional cell carcinomas ($\chi^2 = 26.2$, $P < 0.005$), whereas, single carcinomas (77.6%) showed a predominance of squamous cell carcinoma ($\chi^2 = 22.6$, $P < 0.005$). The tendency of multiple carcinomas to be of the transitional cell type increased with the degree of multiplicity. Thus, the incidence of transitional cell carcinoma was higher (84.4%) in patients with more than four tumors as compared with four or less tumors (46.2%). Of the 19 cases with multiple carcinomas, nine showed tumors of different histologic types in the same bladder.

Gross features of mucosal lesions: The mucosa of the bladder was invariably the seat of various gross lesions. These lesions were the

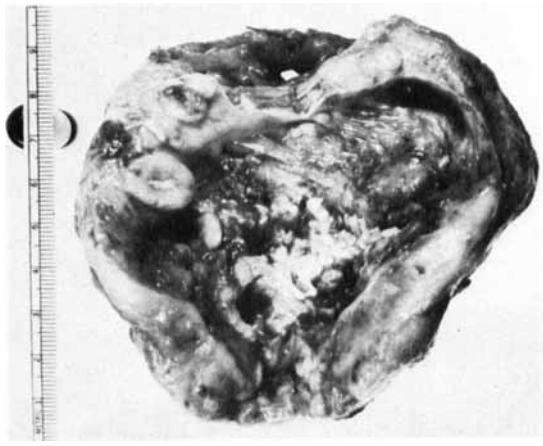

FIG. 2. *Multiple carcinomas of nodular and fibrillary types involving different surfaces of the bladder.*

TABLE 2. Histologic Types and Grades of the 86 Carcinomas

	Squamous		Transitional		Adenocarcinoma	
	No.	Per cent	No.	Per cent	No.	Per cent
Well differentiated	30	45.5	2	11.1	2	2.3
Moderately differentiated	17	25.8	5	27.8	—	—
Poorly differentiated	19	28.8	11	61.1	—	—
TOTAL	66	76.7	18	20.9	2	2.3

TABLE 3. Comparison of Histologic Features of Multiple and Single Carcinomas of Bladder

		Squamous		Transitional		Adenocarcinoma	
	Total no.	No.	Per cent	No.	Per cent	No.	Per cent
Multiple	72	26	36.1	46	63.9	—	—
Single	67	52	77.6	13	19.4	2	3

result of chronic bilharzial cystitis which preceded the development of the carcinoma. Sandy patches were present in 40.7% of the specimens and were due to calcified ova in the submucosa. They appeared as yellowish plaques (Fig. 3) and showed limited mobility over the underlying muscle due to the associated fibrosis. Leukoplakia was found in 27.9% of cases and appeared as white, slightly raised patches (Fig. 4). It was usually flat, but, rarely, verrucous forms were seen. All cases of leukoplakia were observed in association with squamous cell carcinoma only. Cystitis cystica occurred in 18.6% of cases and appeared as multiple microcysts 1–3 mm in diameter. Their color varied from white to dark brown. Bilharzial granulomatous nodules were found in 10.5% of specimens. They were usually sessile and covered with intact mucosa. Chronic bilharzial ulcers were found in only five specimens (5.8%). They were superficial, irregular in outline, with sloping edges and a necrotic yellow floor. The size of these ulcers varied from 1–4 cm in longest diameter.

Histologic features of mucosal lesions: In all the cases studied, there was evidence of Bilharzia ova, mostly *Schistosoma haematobium*. The ova were usually calcified and deposited mainly in the submucosa. The trigone, seminal vesicle, and ureters were less commonly

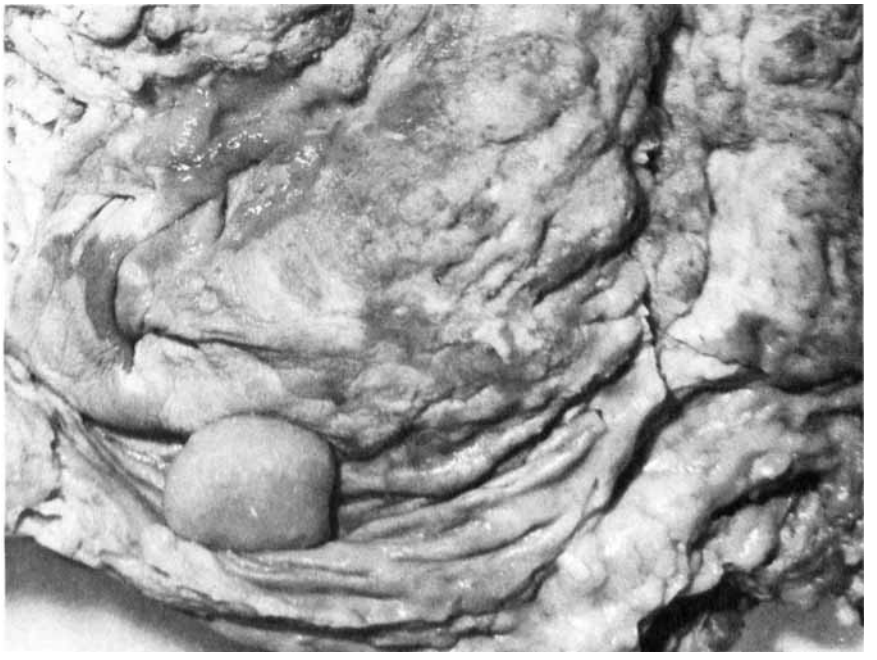

FIG. 3. Sandy patches or superficial ulcers overlying Bilharzia ova in the submucosa and associated vesical stone.

FIG. 4. Leukoplakia of the urinary bladder at the margin of an ulcerative carcinoma.

affected by ova deposition. Sandy patches appeared histologically as dense areas of ova deposition with loss of surface epithelium. Active bilharzial granulomas were observed in 10 out of 86 cases studied. Adult worms of Schistosoma were seen inside veins in five specimens.

The incidence of various epithelial changes in the bladder, as well as in the ureters and urethra, can be seen in Table 4. The distribution of these lesions in the different surfaces of the bladder is shown in Table 5.

Squamous metaplasia was found in the bladder in 65.1% of the specimens. The trigone, urethra, and ureters were less commonly affected. A study of 225 lesions of squamous metaplasia found in 86 specimens was made. Three histologic types of squamous metaplasia were recognized according to the degree of surface keratinization and basal cell hyperplasia. Squamous metaplasia (52.9%) was commonly nonkeratotic (Fig. 5). In 28.9% of metaplastic lesions studied, there was evidence of marked surface keratinization (Fig. 6). Basal cell hyperplasia was present in 18.2% of lesions.

TABLE 4. Epithelial Changes in the Bladder Compared with Those of the Ureters and the Urethra

	Squamous metaplasia		Columnar metaplasia		Carcinoma in situ	
Site	No.	Per cent	No.	Per cent	No.	Per cent
Bladder	56	65.1	45	52.3	35	40.7
Ureters	10	11.6	25	29.0	—	—
Urethra	13	15.1	3	3.5	—	—

Columnar metaplasia of transitional epithelium was observed in 52.3% of bladder specimens. The ureters, trigone, and urethra were rarely affected. By studying 151 of such lesions in the bladder, the three following types were present, usually in association: 1. *surface type,* in which the metaplasia affects the surface epithelium only (observed in 25.8% of the lesions studied); 2. *glandular type, or cystitis glandularis,* in which glandular structures are seen below the surface epithelium, Fig. 7 (observed in 53.6% of lesions), and 3. *cystic type, or cystitis cystica,* which is characterized by microcysts lined by flattened cells and filled with secretions (Fig. 8). This was evident in 20.5% of the lesions.

Carcinoma in situ was found in 35 out of 86 bladder specimens (40.7%). It was least common in the trigone and absent in the ureters and urethra. Histologically, the atypical change involved the whole thickness of the epithelium, but there was no infiltration of the subepithelial stroma. This lesion was observed in both surface epithelium and in cell nests of Brunn (Figs. 9 and 10).

Forty-five patches of leukoplakia identified by gross examination were examined histologically for evidence of metaplastic or atypical lesions. In 44.4% of cases, there was squamous metaplasia only (Table 6). In 35.6% of cases, there was evidence of carcinoma in situ in addition to metaplasia. Infiltrative carcinoma was present in 20% of leukoplakia.

TABLE 5. Distribution of Mucosal Lesions in Different Surfaces of the Bladder

	No. of surfaces	Squamous metaplasia		Columnar metaplasia		Carcinoma in situ	
		No.	Per cent	No.	Per cent	No.	Per cent
Vault	76	31	40.8	12	15.8	12	15.8
Anterior	81	28	34.6	13	16.0	9	11.1
Right lateral	83	33	39.8	24	28.9	13	15.7
Posterior	84	34	40.5	28	33.3	15	17.9
Left lateral	85	35	41.2	17	20.0	13	15.3
Trigone	83	26	31.3	8	9.6	5	6.0

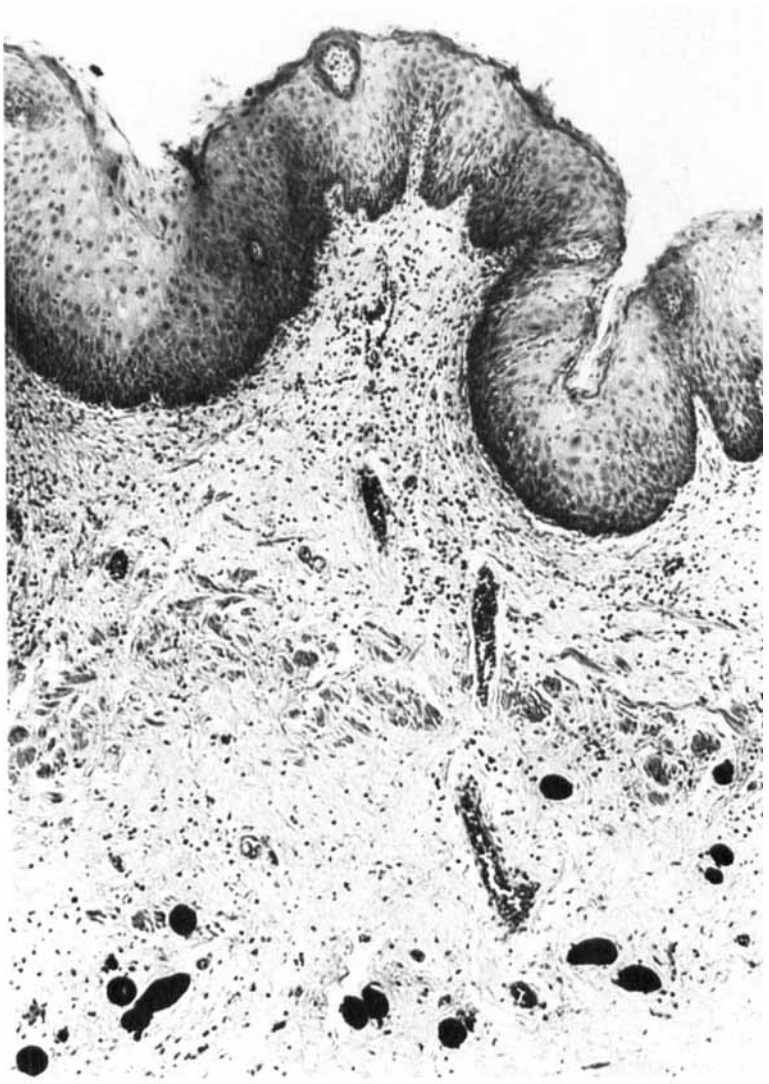

FIG. 5. Nonkeratotic squamous metaplasia of surface urothelium and calcified Bilharzia ova in the submucosa (H and E, ×100).

Squamous cell carcinoma, in contrast to other types, was commonly associated with squamous metaplasia as shown in Table 7. Gross leukoplakia was found in 36.2% of squamous cell carcinoma. Conversely, by comparing the incidence of columnar metaplasia in squamous and transitional cell carcinoma, it was found to be not significantly different (test of proportions, $P < 0.05$). The two cases of adenocarcinoma were both associated with columnar metaplasia.

The mucosal lesions associated with multiple and single carcinomas are presented in Table 8. The association of carcinoma in situ with multiple carcinomas (68.4%) was statistically significant ($\chi^2 = 6.4$, $P < 0.025$) as compared with single tumors (32.8%), whereas the association of squamous metaplasia with multiple and single carcinomas was insignificant ($\chi^2 = 0.013$, $P > 0.05$).

DISCUSSION

Previous reports on carcinoma of the bilharzial bladder have referred to the frequent occurrence of metaplastic epithelial changes.[4,6] However, a higher incidence of these lesions was found in the present study due to examination of more tissue sections from the specimens. These lesions showed a rather uniform distribution in the bladder, but were strikingly rare in the trigone, ureters, and urethra. This may possibly be due to difference in embryologic origin. Carcinomas of the nonbilharzial bladder are also associated with a similar spectrum of metaplastic and atypical

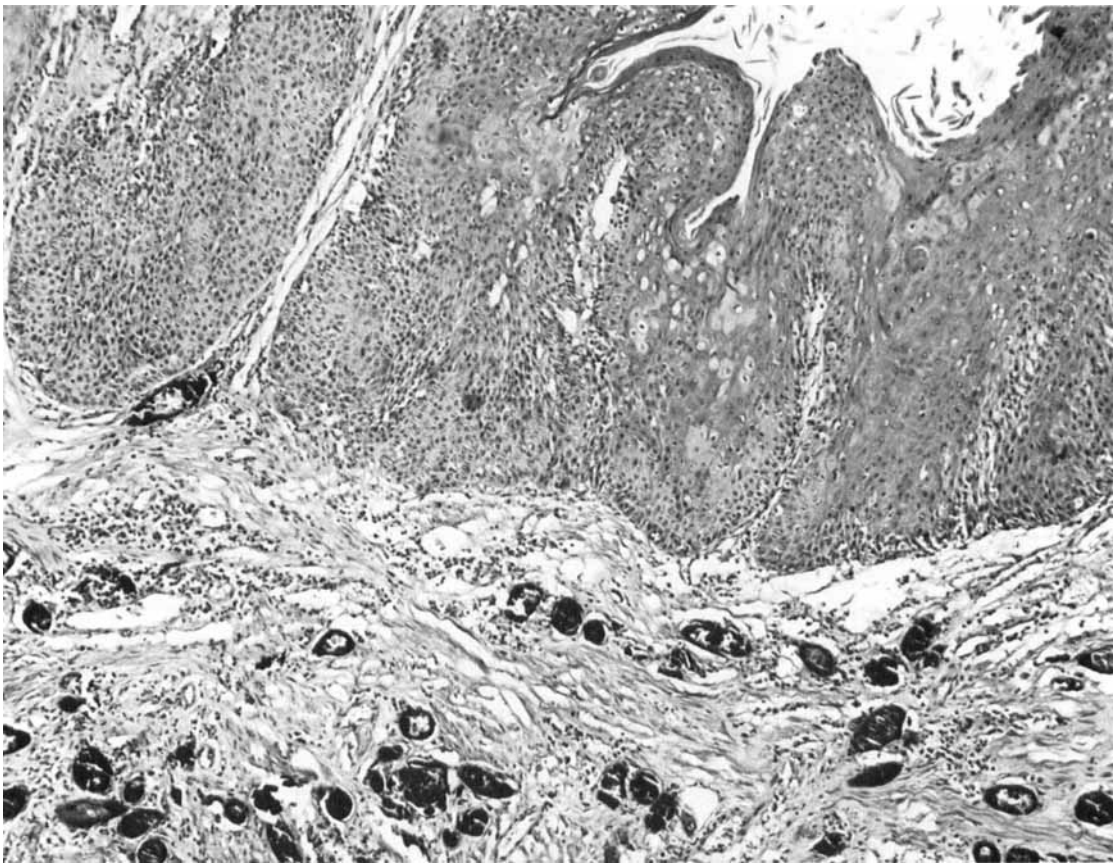

FIG. 6. Squamous metaplasia with atypical hyperplasia of basal layer (H and E, ×70).

lesions,[8] but their incidence appears to be less common compared with the bilharzial cases.[9] In a series of 100 transitional cell carcinomas reported by Shade, a study of biopsy specimens from the relatively normal mucosa revealed abnormal lesions in about 80% of cases.[12] Squamous metaplasia occurred in 2%, cystitis glandularis in 20%, atypical transitional epithelium in 42%, and carcinoma in situ in 30%.

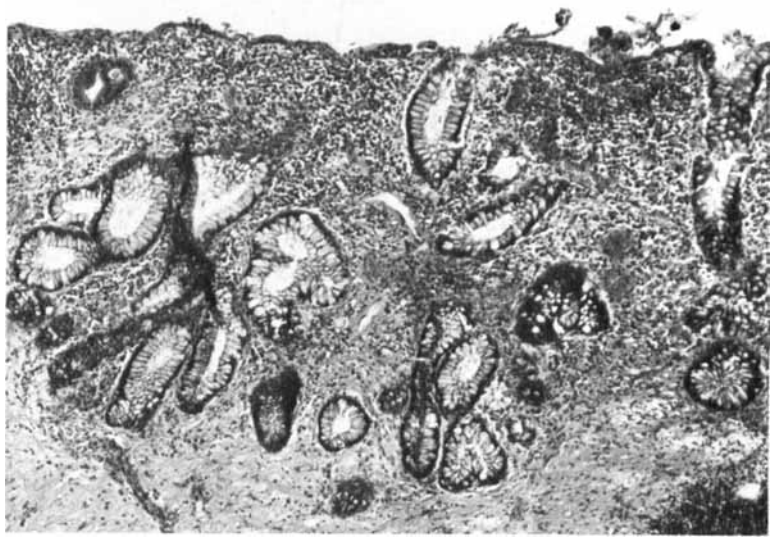

FIG. 7. Cystitis glandularis showing glandular structures lined by columnar cells (H and E, ×90).

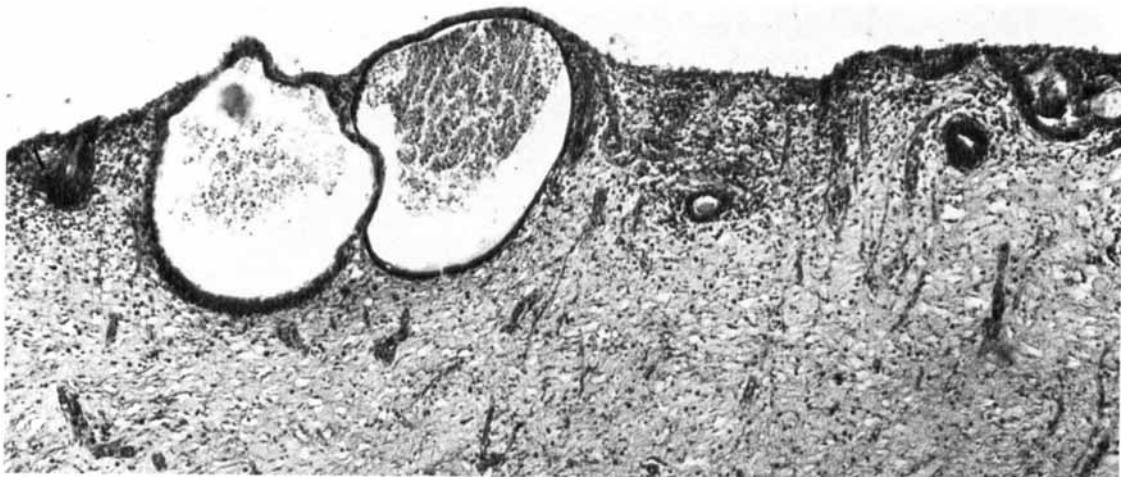

FIG. 8. Cystitis cystica showing small cysts lined by flat cells (PAS, ×90).

The usual terminology of metaplastic lesions of the bladder was slightly modified in the present study. Cystitis glandularis and cystitis cystica were considered stages in one basic process indicating columnar metaplasia. Furthermore, the term leukoplakia was used only as a gross description. Histologic lesions showing hyperkeratosis and basal cell activity, which are commonly called leukoplakia by some authors,[6] were included in this study under squamous metaplasia.

Gross leukoplakia was found in association with squamous cell carcinoma. Histologic study of patches of leukoplakia showed a variety of histologic lesions of different biologic behavior, i.e., squamous metaplasia, carcinoma in situ, and infiltrative carcinoma. In about 20% of cases, there were infiltrative carcinomas in these lesions. Accordingly, patches of leukoplakia of the bladder should be excised and submitted to pathologic examination.

In the present series, a high incidence of squamous cell carcinoma (76.7%) and a relatively rare site of origin from the trigone (2.3%) were observed. This is in marked contrast with carcinoma of the nonbilharzial bladder in which the squamous type occurs in 18.4%, with origin from the trigone in 21%.[9] The squamous cell carcinomas of the present series showed a uniform squamous differentiation in all parts of the carcinoma, whereas in reports on the nonbilharzial bladder cancer, squamous cell carcinoma usually refers to poorly differentiated transitional carcinoma with focal areas of squamous metaplasia. A distinction of these two types is important since their behavior is different. Squamous cell carcinoma is usually slow growing and associated with good prognosis, whereas metaplastic tumors are anaplastic and aggressive in behavior.[10,13] A true squamous carcinoma in the nonbilharzial bladder carcinoma occurs in only 1.6% of cases,[10] but if transitional carcinomas with metaplastic tendency are included, the incidence rises to 18.4%.[9]

A study of the associated metaplastic lesions with each type of carcinoma helped to clarify this peculiar feature of bilharzial bladder cancer. The predominance of squamous cell cancer is possibly due to the frequent squamous metaplasia in the bilharzial bladder. As shown, the overall incidence of squamous metaplasia was high in the bilharzial bladder (65.1%) and was more commonly associated with the squamous cell carcinoma (81.8%) than with transitional cell carcinoma (16.7%). The two cases of adenocarcinoma reported in this study were both associated with columnar metaplasia. It is probable that metaplasia is not a precancerous lesion per se, but it does determine the type of carcinoma if such develops in the bilharzial bladder. Conversely, carcinoma in situ is a lesion of more malignant potentiality and probably precedes invasive carcinoma. Its incidence was strikingly high in bilharzial bladder cancer (40.7%) as compared with previous reports (23%).[6] It is interesting to note that the trigone, ureters, and urethra, which are rare sites of cancer as shown in the present study, were also rarely affected by carcinoma in situ.

There are few reports in the literature about the incidence of multiple carcinomas of

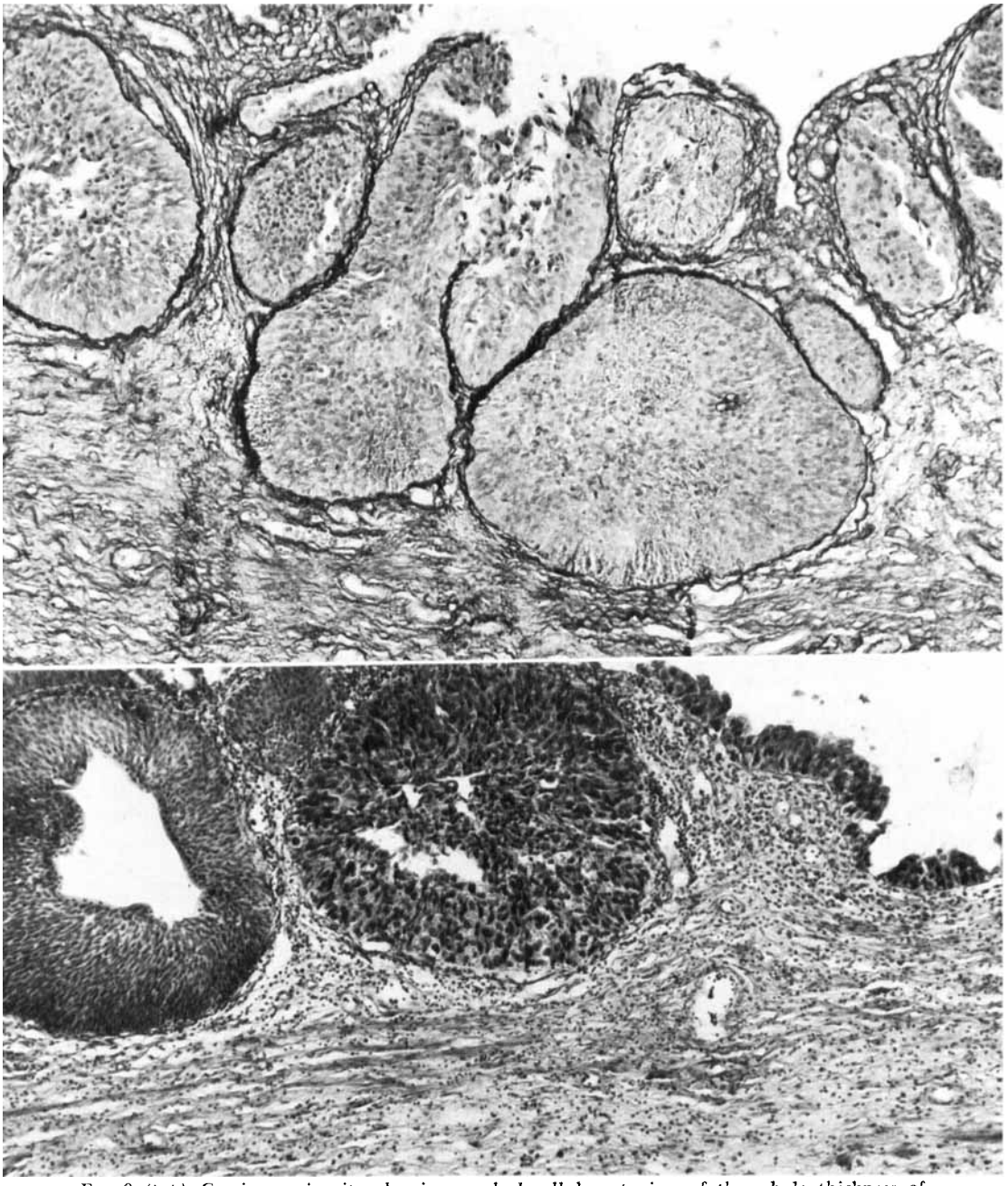

FIG. 9 *(top)*. Carcinoma in situ showing marked cellular atypism of the whole thickness of urothelium but absence of infiltration of the underlying stroma (Wilder's reticulum stain, ×90).

FIG. 10 *(bottom)*. Carcinoma in situ involving a cell nest of Brunn showing large, hyperchromatic and irregular nuclei. The other cells to the right with small and uniform nuclei are only hyperplastic (H and E, ×120).

the bilharzial bladder. El-Sebai reported an incidence of 6% in the 350 cases studied.[5] Ishak et al. detected 10 multiple carcinomas out of 91 cases of bilharzial bladder cancer, an incidence of 10.1%.[6] In the present series, the incidence was 22.1%. This relatively high incidence compared with previous reports is due

TABLE 6. Histologic Diagnosis in 45 Lesions of Leukoplakia

Lesion	No.	Per cent
Squamous metaplasia	20	44.4
Carcinoma in situ	16	35.6
Infiltrative carcinoma	9	20.0
TOTAL	45	

TABLE 7. Mucosal Lesions in Relation to the Type of Vesical Carcinoma

Type	No. of tumors	Columnar metaplasia		Squamous metaplasia		Carcinoma in situ	
		No.	Per cent	No.	Per cent	No.	Per cent
Squamous cell carcinoma	66	35	35.0	54	81.8	31	47.0
Transitional	18	8	44.4	3	16.7	4	22.2
Adenocarcinoma	2	2					

to the more thorough survey of the bladder mucosa by both gross and histologic study. All these data represent simultaneous lesions identified in the same specimens. Our figures are very close to those reported by Mostofi (24%) in the nonbilharzial bladder.[7]

The observation of multiple carcinomas in the bladder may be explained by multicentric origin, implantation to intact or ulcerated mucosa, and submucous lymphatic spread from the primary carcinoma. In the present study, the spread through submucosal lymphatics was excluded by histologic examination of the mucosa intervening between the multiple carcinomas, which showed no evidence of infiltration. Successful implantation over an intact mucosa had been demonstrated in isolated bladder pouch in dogs.[7] However, implantation through an intact mucosa in the presence of urine stream appears improbable due to unphysiologic and mechanical factors. The multiple tumors reported in this study are probably multifocal in origin. This is supported by the high incidence (47.4%) of tumors of different histologic types and the high association of carcinoma in situ with multiple as compared with single tumors. A urinary carcinogen possibly plays a role in the genesis of multiple bladder tumors. Thus, increased amounts of abnormal tryptophan metabolites in urine have been demonstrated in patients with heterotopic recurrences[12] of bladder cancer.

TABLE 8. Mucosal Lesions Associated with Multiple and Single Carcinomas

	No. of cases	Squamous metaplasia		Carcinoma in situ	
		No.	Per cent	No.	Per cent
Multiple	19	13	68.4	13	68.4
Single	67	47	70.1	22	32.8
TOTAL	86				

The relatively high incidence of carcinoma in situ and multiple carcinomas have practical application in the surgical treatment of carcinoma of the bilharzial bladder. Radical total cystectomy is recommended. However, local removal is only justifiable for early single tumors. In such cases, adequate follow-up by cystoscopy and urine cytology is essential for early detection of newly developing lesions.

The mechanism of evolution of the metaplasia and neoplasia in the bilharzial bladder is still poorly understood. Carcinogenic agents excreted in urine possibly play a doubtful role. In experimental animals, lesions are produced by local application of carcinogens in the bladder.[3] The various proliferative and neoplastic changes in mouse bladder epithelium, in response to prolonged irritation, has been studied by Roe.[11] The carcinogenic products of abnormal tryptophan metabolism which are reported in the nonbilharzial bladder were also found in the bilharzial cases.[1] Multiple factors are probably involved in bilharzial bladder carcinogenesis. Chronic cystitis, local irritation by Schistosoma ova, nutritional and metabolic factors may also play a role. Further experimental studies in this field are needed.

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