

CARCINOMA OF BILHARZIAL BLADDER

Diagnostic Value of Urine Cytology

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ABSTRACT—The diagnostic accuracy of cytologic study of urine was evaluated by cytohistopathologic correlation. Samples were processed by sedimentation then centrifugation. Papanicolaou-stained smears as well as cell blocks were examined. In 183 patients with carcinoma of the bladder results of cytologic examination were positive in 90 per cent, inconclusive in 7 per cent, and negative in 3 per cent. Unsatisfactory smears (inconclusive and negative), were due to hypocellularity, associated sepsis, or hemorrhage. Measures to overcome these difficulties were discussed. The high diagnostic accuracy in this series is due to technical improvements and the predominance of squamous carcinoma which is easy to recognize cytologically. Cytologic study of urine is an accurate method for diagnosis and possibly valuable for detection of carcinoma of the bilharzial bladder.

Carcinoma of the urinary bladder is the commonest malignant tumor affecting men in Egypt.¹ It is usually preceded by chronic bilharzial infestation and exhibits distinct clinical and pathologic features.^{2,3}

Previous reports on the value of cytologic study of urine in the diagnosis of carcinoma of the bilharzial bladder are controversial. Some investigators reported that cytodagnosis of carcinoma of the bilharzial bladder is difficult and rather inaccurate.^{4,6} Others gave highly satisfactory results.⁷⁻⁹

The aim of this study is to evaluate the accuracy of cytologic diagnosis in a large series of cases and to correlate the results with histopathologic findings.

Material and Methods

The present report is based on examination of single urine specimens obtained from 183 patients with carcinoma of the bladder. All of these

patients gave a history of bilharziasis and received various courses of antibilharzial therapy but were not previously treated by surgery or irradiation. Tissues for histopathologic studies were obtained by cystoscopic biopsy and/or from the surgical specimens.

Freshly voided urine in volumes up to 250 ml. were placed in a conical glass container and left for one hour to allow sedimentation of cellular constituents. The upper part of the specimen was discarded. From the remainder, a sample of 50 ml. was centrifuged in a glass tube for five minutes at 1,500 r.p.m. Two drops from the sediment were smeared on two microscopic slides by means of a glass rod. The slides were previously coated with 2 per cent gelatin solution and allowed to dry. This greatly helped the cells to adhere to the glass, with minimal cell loss during staining. The smears were fixed immediately in 90 per cent ethyl alcohol for twenty minutes. Recently we utilized Carnoy's fixative (10 per cent acetic acid and 30 per cent chloroform in absolute ethyl alcohol); this had the advantage of eliminating red blood cells in samples associated

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TABLE I. Accuracy of cytologic diagnosis correlated with tumor type

Pathologic Diagnosis Type	Pathologic Diagnosis		Cytologic Diagnosis					
	Number	Per Cent	Positive		Inconclusive		Negative	
			Number	Per Cent	Number	Per Cent	Number	Per Cent
Squamous	129	70.5	124	96	5	3.9	...	0
Transitional	38	20.8	33	87	4	10.5	1	2.5
Adenocarcinoma	12	6.5	7	58	3	35	2	17
Unclassified	4	2.2	1	25	1	25	2	50
TOTALS	183		165	90.1	13	7.1	5	2.7

with hemorrhage. The smears were stained by the Papanicolaou method.

Cell blocks were made from the remaining part of the sediment by fixation with Carnoy's solution, followed by paraffin embedding. Serial sections were then made and stained with hematoxylin and eosin.

The millipore filter technique was tried in a few cases.¹⁰ Its use proved to be unsatisfactory in our patients because of the frequent blockage of filters by abundant pus cells.

Results

Results of cytologic examination of 183 patients with cancer of the bladder showed an over-all accuracy of 90.1 per cent. The results were negative in 5 cases (2.7 per cent) and inconclusive in 13 (7.1 per cent).

The accuracy of cytologic diagnosis was correlated with the histopathologic type of the tumor (Table I). The frequency of a correct cytologic diagnosis was higher in association with squamous-cell tumors (96 per cent) and lowest with anaplastic tumors (25 per cent). The accuracy of the cytologic examination in the determination of the tumor type was also explored in 165 patients with positive cytologic diagnosis (Table II). Cytologic study could provide correct typing in 87.8 per cent of cases.

Squamous cell carcinoma was the commonest tumor encountered in this series (70.5 per cent). Cytologically, it was characterized by abundant exfoliation of cells, either separate or arranged in groups. Cytoplasmic keratinization, sharp refractile cell borders, and hyperchromatic nuclei were the distinctive features of the cells of this tumor. Malignant cell nests, with concentric arrangement of cells, were encountered in 71 per cent of cases (Fig. 1A and B). Small nests, composed of only two cells, were observed as a "cell-in cell" pattern (Fig. 1C). Separate cells with abnormal shape and size were abundant.

These included spindle cells and tadpole cells (Fig. 1D to F). Small rounded keratin bodies were found extracellularly or as intracytoplasmic inclusions (Fig. 1G).

With transitional cell tumors the cells were mainly exfoliated in light clusters with little cytoplasm (Fig. 1H). The number of exfoliated cells in adenocarcinoma was few, and most cases were mistyped as transitional or anaplastic. The diagnosis of adenocarcinoma was possible when the cells were arranged around a central lumen (Fig. 1I). The vacuolated cytoplasm or eccentric nuclei also helped in typing this tumor.

Comment

Cytologic examination of urine provided an accurate means of diagnosis of cancer of the bilharzial bladder in 90 per cent of cases in the present series. This result was based on examination of single urine specimens. A comparison between our data and previous reports is given in Table III. The high diagnostic accuracy in this series may be attributed to the use of cellular concentration by sedimentation, and the conjoint use of cell block technique with cytologic smears. In addition, gelatin coating of the slides markedly diminished cell loss during staining.

The diagnostic accuracy varied according to tumor type, being highest with squamous-cell carcinoma (95 per cent). This can be explained by the fact that squamous-cell carcinoma associated with bilharzial bladder is commonly of the well-differentiated type, a tumor which is easily recognized cytologically.^{2,3} On the other hand, adenocarcinoma and anaplastic tumors presented a diagnostic difficulty. In adenocarcinoma, the number of exfoliated cells was few. This finding was also experienced by Johnson.¹¹ Anaplastic carcinomas were commonly associated with extensive hemorrhage which concealed malignant cells.

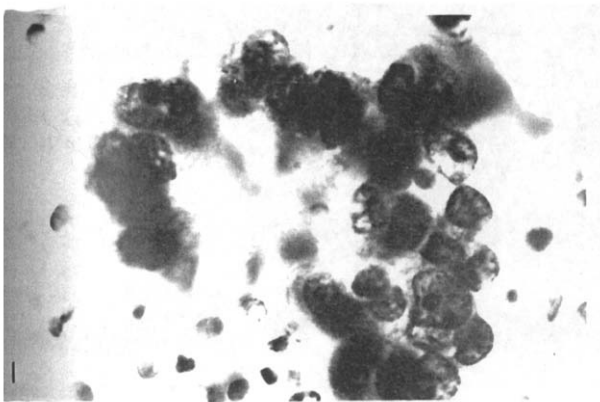
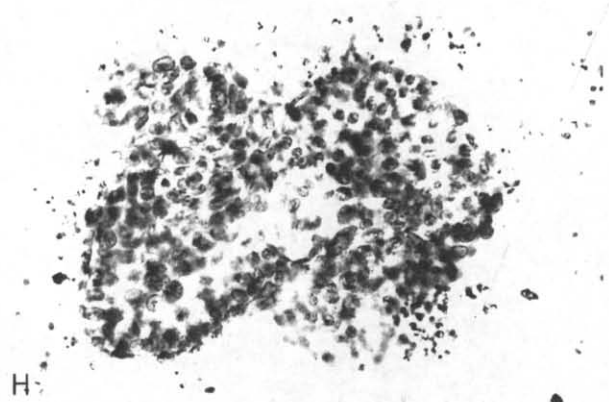
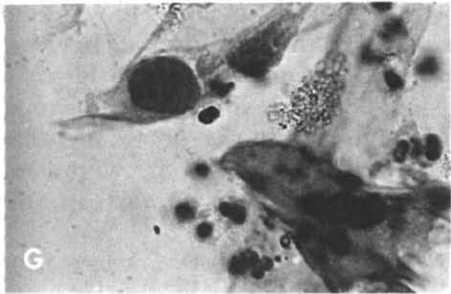
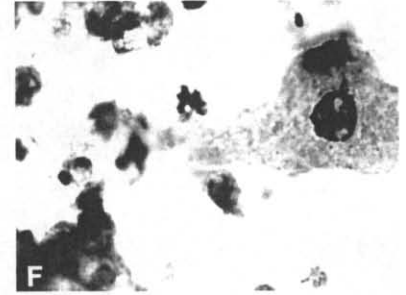
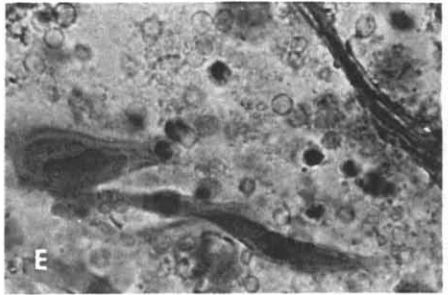
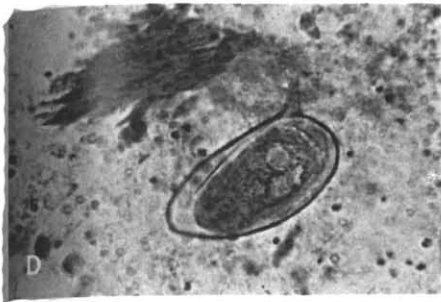
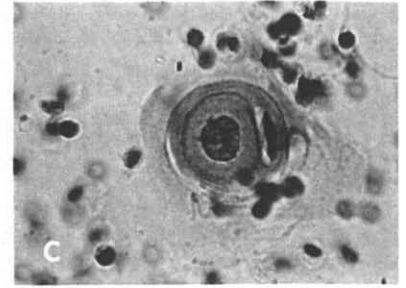
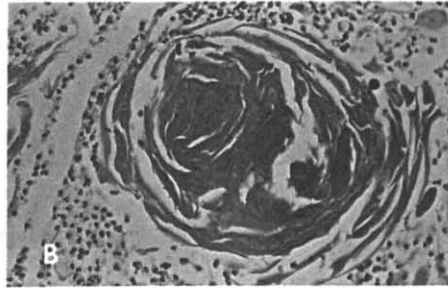
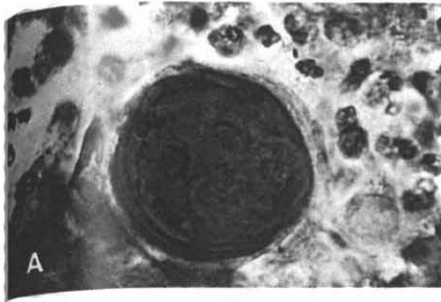


FIGURE 1. Malignant cell nest of squamous carcinoma (A) in smear, (B) in cell block. (C) "Cell-in cell" pattern. (D and E) Malignant spindle cells, (D) with bilharzia ova, (E) note refractile borders. (F) Tadpole cell with expanded cytoplasm at one end of cell. (G) Intracellular keratin inclusion. (H) Cell cluster of transitional carcinoma. (I) Adenocarcinoma cells arranged around central lumen.

TABLE II. Accuracy of urine cytologic diagnosis in tumor typing*

Pathologic Diagnosis	Number	Number of Cytologic Diagnoses				Correct Typing (Per Cent)
		Squamous	Transitional	Adenocarcinoma	Anaplastic	
Squamous	129	119	6	92.9
Transitional	38	6	20	3	9	52.6
Adenocarcinoma	12	2	5	2	3	16.6
Anaplastic	4	...	1	1	2	50.0

*Total number of cases with correct typing, 143 (81.8 per cent).

TABLE III. Cytologic diagnosis of carcinoma of bilharzial bladder

Author	Number of Cases	Positive Per Cent	Inconclusive Per Cent	Negative Per Cent
Elwi, F'am, and Ramzy (1962) ⁵	42	26.1	7.1	66.7
Riad and Abdel-Wahab (1970) ⁷	41	87.8	7.3	4.9
Halawani, Al-Waidh, and Said (1970) ⁸	52	91.3	...	7.7
Kamcl, Mooro, and Kamel (1971) ⁹	67	76.1	19.4	4.5
Present series	183	90.1	7.1	2.7

The frequency of false-negative and inconclusive smears was 2.7 and 7.1 per cent, respectively. Hypocellularity, associated sepsis, and hemorrhage were the main underlying causes. Repeated cytologic examination of multiple urine samples was required for these cases. Riad and Abdel-Wahab⁷ and Kamel, Mooro, and Kamel⁹ found that examination of multiple samples was associated with a higher diagnostic accuracy. Again, specimens obtained by catheter irrigation may be resorted to, since this results in a maximum yield of malignant cells.¹² Elimination of pus cells by using wide-pore filters is now under trial. Fixation of the smears in Carnoy's solution was helpful in cases associated with hemorrhage.

The frequency of false-negative diagnosis of cancer was 3 per cent. This error was made only in nonsquamous carcinomas. The error could be due to various factors, such as, exfoliation of degenerated tumor cells, loss of cells during staining, or their masking by other cellular constituents in urine. To minimize the false-negative errors, patients with strong clinical suspicion of cancer should be subjected to repeated cytologic examination by studying both spontaneously voided urine as well as catheter irrigation samples.

Our results compare favorably with similar reports on nonbilharzial tumors. In a review of

previous literature Umikar¹³ reported that the diagnostic accuracy was found to vary from 26 to 100 per cent, with a mean of 72 per cent. This wide range of accuracy was due to the heterogeneity of the cases studied. Some reports included benign papillomas, others included renal and ureteric tumors, and some were concerned with detection of early tumors in industrial workers.

The results of the present work are encouraging for the future use of this technique in screening of patients with bilharzial bladder, within the high risk age group. It is hoped that the application of such screening programs could be of value in the detection of tumors at an early stage and the improvement of the present results of treatment.

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