



## Original Article

# Diagnostic Value of Exfoliative Cytology of Voided Urine in the Detection of Urothelial Cancers

S M Badruddoza<sup>1</sup>, F A Azim<sup>2</sup>, A J E Nahar Rahman<sup>2</sup>, M Kamal<sup>2</sup>  
A R Barua<sup>2</sup>, K H Khan<sup>2</sup>, T Chowdhury<sup>3</sup>

### Abstract

Carcinoma of the urinary bladder (urothelial carcinoma) affects men more often than women at a ratio of 3:1 to 4:1. Besides many other invasive diagnostic tools, cytological examination of voided urine is the technique for diagnosis of urothelial carcinoma in its preclinical phase long before its cystoscopic & radiographic/ imaging recognition. In this study, a total of 57 were taken to see the diagnostic accuracy of voided urine cytology in the diagnosis of urothelial carcinoma. Out of 57 cases, 53 (92.99%) were given positive for malignancy and 4 (7.01%) were negative. Histologic diagnosis was 14 (24.56%) non invasive papillary tumors, 1 (1.76%) carcinoma in-situ and 42 (73.68%) invasive carcinomas. Of 14 grade II non invasive papillary tumors, 12(85.72%) were positive cytologically. Of 42 cases of invasive carcinoma, 2 were negative and 100% positive cytology was noted in 1 case of carcinoma in-situ. For all low-grade tumors, the sensitivity was about 85.72% and for all high-grade tumors, it was about 95.34% with a sensitivity of 100% and 95.24% for flat CIS and invasive carcinomas respectively. For all tumors the sensitivity was 92.99%. The specificity was 100% since there were no false positive cases. The diagnostic accuracy was 93% (approximately) Consistent with previously published data, this study showed the highest diagnostic accuracy with high grade tumors and lowest with low grade tumors with maximum invasion limited to the lamina propria. Voided urine cytology purely a non invasive, simple, cheap, easy to perform technique can be done as a first line cost effective method in the diagnosis of urothelial carcinoma particularly in a developing country like Bangladesh.

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### Introduction

Carcinoma of the urinary bladder affects men more often than women at a ratio of 3:1 to 4:1.<sup>1</sup> Most cases presents in patients over the age of 50 years. But they can also occur in younger adults and children. Transitional cell carcinoma (TCC) comprises about 90% of all primary tumor of urinary bladder, about 75% of these tumors arises

in the region of trigone, though they can also be located else where in the bladder mucosa.<sup>2</sup>

The urothelial tumors may be papillary or non-papillary (flat) and invasive or in-situ (noninvasive).<sup>3,4</sup> Transitional cell carcinoma of the urinary bladder is generally divided into three groups: superficial papillary, carcinoma in-situ and

<sup>1</sup> Professor, Department of Pathology, Rajshahi Medical College, Rajshahi.

<sup>2</sup> Professor, Department of Pathology, BSMMU, Dhaka.

<sup>3</sup> Associate Professor, Department of Pathology, BSMMU, Dhaka.

invasive. Superficial bladder tumors are largely grade-I or II papillary transitional cell carcinomas that may or may not invade the lamina propria.<sup>5</sup> Usually non-invasive lesions are often referred to as “superficial” to differentiate them from carcinoma in-situ (C.I.S).<sup>4</sup>

The urothelial tumors may be classified into two fundamental although, to some extent overlapping groups with different behavioral patterns and prognosis: the low grade papillary tumors, rarely capable of invasive growth and the high grade tumors, papillary or non papillary, usually capable of invasive growth, hence metastases.<sup>6,7</sup> Depending on the degree of epithelial abnormality, urothelial tumors are graded from I to III.<sup>6</sup>

The prognosis of papillary tumors depends not only on the grade of tumor abnormality but also on the level of histologic abnormality of the urothelium peripheral to the visible lesion.<sup>6,8</sup> The low-grade tumors such as papilloma or grade-I tumors are less likely to be followed by new tumors than are tumors of grade II or III. The non-papillary tumors of the urothelium have a natural history different from the papillary tumor.<sup>6</sup>

Low grade tumors (such as papilloma, grade I tumors and some grade II carcinomas) very rarely progress to invasive cancer whereas high-grade tumors (C.I.S, some carcinomas grade II and all carcinomas of grade III) often lead to invasive and metastatic carcinoma.<sup>9,10</sup>

It has now been documented that in about 80% of the cases, primary invasive carcinoma of the bladder are not preceded by papillary tumors, hence the conclusion that most of these tumors are derived from invisible and asymptomatic flat lesions namely carcinoma in-situ. In approximately 20% of cases of invasive carcinoma preceded by papillary tumors, it has been documented by mapping the urinary bladder that invasive cancer is usually derived not from the papillary tumors but from adjacent epithelial segments showing abnormalities consistent with carcinoma in-situ or related lesions.<sup>6,8,11</sup>

The principal features of carcinoma in-situ of the urinary bladder are that cystoscopically it may mimic inflammation or there may be no

cystoscopic abnormality whatsoever. The most important property of flat carcinoma in-situ is its ability to progress to invasive carcinoma. If untreated, carcinoma in-situ will progress to invasive carcinoma in at least 60% of all patients within 5 years. Because the lesions produces only non-specific symptoms or may be asymptomatic, its diagnosis is based either on cytology of voided urine or on incidental biopsies of bladder epithelium.<sup>6</sup>

One of the major accomplishments of urine cytology is the detection of urothelial carcinoma in its preclinical phase, long before its cytoscopic and radiographic recognition.<sup>12</sup> Cytological examination of voided urine is the technique of choice for detection, diagnosis and follow up of tumors of the lower urinary tract. The most important value of cytology of voided urine is the diagnosis of clinically unsuspected case of carcinoma particularly carcinoma in-situ.<sup>13</sup>

The usefulness of application of cytologic techniques to urinary tract are:

1. Detection and diagnosis of tumors and precancerous states of the urinary tract other than well-differentiated papillary lesion.
2. Monitoring of patients treated for neoplastic lesion of lower urinary tract.
3. Follow up of high risk asymptomatic individual workers exposed to known carcinogens.<sup>6</sup>

Moreover cytological examination of voided urine is the only totally harmless non-invasive method,<sup>13,14</sup> easy to obtain<sup>14</sup> and can be done on an outpatient basis.<sup>15</sup> Cytology has the distinct advantage of sampling of entire urothelial mucosa.<sup>3</sup> The simplicity, convenience and accuracy of multiple voided urine cytology justifies its continued use as a first line diagnostic and detection technique.<sup>14</sup>

In summary, it may be concluded that urinary cytology can be a useful diagnostic adjunct in the study of patients with transitional cell carcinoma.<sup>16</sup> and in the clinical setting, urine cytology and cystoscopy complement each other as diagnostic tools, cytology adding greatly to the clinicians

ability to detect occult and particularly high grade bladder tumors.<sup>17</sup>

### **Aims and Objectives**

This study is designed to see the accuracy of voided urine cytology in the diagnosis of malignant tumors of urinary bladder (Urothelial cancers.)

### **Material and Methods**

The study was carried out in the Department of Pathology, B.S.M.M.U. Dhaka, during one year period.

**A. Selection of the Patients:** A total of fifty seven patients clinically suspicious of having urinary bladder malignancy or histologically confirmed patients, admitted in the Urology Department of B.S.M.M.U., D.M.C.H. and private clinics were included in this study. All necessary and relevant information regarding patients were recorded methodically and meticulously as far as possible.

### **B. Cytological Examinations:**

**1. Selection of Specimens:** From all patients at each admission, the diagnostic work up included cytological examinations of three samples of morning's second voided urine. Voided urine is the specimen of choice for all screening program and for diagnostic studies because of the ease of collection and satisfactory results.<sup>3</sup>

Morning urine specimens have the advantage of highest cellularity but also the disadvantage of marked cell degeneration.<sup>6</sup> A specimen from the morning's second voiding is usually best. Three samples obtained on three consecutive days are diagnostically optimal.<sup>3,6,13</sup> L.G. Koss and associates in a study of 151 positive cases mentioned that the cytological diagnosis was established on the first specimen in 79%, on the second specimen in an additional 14% and on the third specimen in 7% of cases. These results justify the use of three consecutive daily urine specimens for optimal diagnostic results.<sup>13</sup>

**2. Sample Preparations:** Urine samples should be sent to the laboratory within three hours of collection. Processing should proceed without delay if the specimen is received unfixed.<sup>18</sup> Fifty (50) ml of urine specimen is centrifuged at 10g for 5-10 minutes, the supernatant decanted and the pellet is directly smeared on glass slides.<sup>14</sup> Albuminized slides are recommended for better attachment of cells to the slides.<sup>3,6,19,20,21</sup> In direct smear technique, after permitting the smear to dry only partially around their edges (also for the purpose of better adhesion), the slides were fixed in 95% ethyl alcohol.<sup>20</sup> There, the slides may be kept for any length of time although a fixation of 5-10 minutes is sufficient.<sup>19</sup> The slides are then stained with Papanicolaou method.<sup>3,5,6,13,20,21</sup>

**3. Pattern of Smears (Smear criteria):** The smears undergoing cytological examination were diagnosed as:

- a. Negative: It includes cytological specimens with no abnormal cells or with non-suspicious features of reactive or degenerative changes.
- b. Atypia or Atypical: The diagnosis of atypical was rendered when an alteration of cell morphology thought to be benign was observed. Mildly atypical cells with non-suspicious nuclei showing regular chromatin and euchromatin and varying cytoplasmic changes are due to chemotherapy, radiotherapy or any other irritation of the urothelium.
- c. Suspicious: This diagnosis is rendered when the evidence was judged to be strongly suggestive of cancer but insufficient for an outright diagnosis.
- d. Positive or malignant cells present: Case in which a definitive cytologic diagnosis of cancer had been made with an indication of probable cell type was considered "positive". Malignant cells showed large hyperchromatic nuclei with coarse chromatin and often occurred in clusters.

- e. Non diagnostic or unsatisfactory: A smear is judged to be non diagnostic or unsatisfactory when the cellular content is extremely low for assessment, the cells were obscured by inflammatory cells, R.B.C or debris, when samples were highly contaminated with bacteria, when the specimen is poorly preserved or when preparation and /or staining errors were obvious. These slides should not be diagnosed as negative but should be returned as unsatisfactory, inadequate or insufficient for diagnosis.

Finally the negative and atypical diagnoses were combined in to one group (cytologic negatives) and the suspicious and positive diagnoses were combined in to a second group (cytologic positives).<sup>9,10,13,16,22,23</sup>

## Results

The purpose of the present study is to see the diagnostic accuracy of voided urine cytology in the diagnosis of urinary bladder malignancy. It is of particular interest to see how a simple test can be helpful as one of the powerful diagnostic tools in the detection and diagnosis of different malignant tumors of the urinary bladder.

A total of 57 cases were collected from the Urology Departments of the B.S.M.M.U., D.M.C.H. and private clinics during one year period.

### Cytologic diagnoses in 57 cases

There were no atypical, suspicious or unsatisfactory cases. Out of 57, 53 (92.99%) were given positive for malignancy and 4 (7.01%) were negative.

**Table I :** Cytologic diagnosis of 57 cases.

No.	Cytologic diagnosis	No. of cases	Percentage
1.	Negative	04	7.01%
2.	Atypical	00	00%
3.	Suspicious	00	00%
4.	Positive	53	92.99%
5.	Unsatisfactory	00	00%
	<b>Total</b>	<b>57</b>	<b>100%</b>

The histologic diagnoses of 57 cases were 14 (24.56%) non-invasive papillary tumors, 1 (1.76%) carcinoma in-situ and 42 (73.68%) invasive carcinomas of all grades and types.

There were no grade-I and grade-III non-invasive papillary tumors in this series. Of 14 grade-II non-invasive papillary tumors, 12 (85.72%) were cytologically positive. With only two exceptions, out of 42 all of the invasive carcinomas of all grades and types were identified by cytology as cancerous. A 100% positive cytology was noted in the detection of flat carcinoma in-situ.

Of the 43 high-grade lesions (comprising grade-III papillary lesions, invasive carcinomas and flat carcinomas in-situ), 41 (95.34%) gave positive cytologic results. Of the total 57 cases of malignant lesions of urinary tract, 53 (92.99%) were positive on cytological examination.

### Diagnostic Sensitivity and Specificity of Cytologic Diagnosis

Table II shows sensitivity, specificity and accuracy of voided urine cytology. For all low-grade tumors the sensitivity was about 85.72% and for all high-grade tumors, it was about 95.34% with a sensitivity of 100% and 95.24% for flat CIS and invasive carcinomas respectively. For all tumors the sensitivity was 92.99%. The specificity was 100% since there were no false positive cases. The diagnostic accuracy was 93% (approximately).

**Table II:** Diagnostic sensitivity and specificity of cytologic diagnosis.

Type of Lesion	No +	True +	True -	False +	False -	Sensitivity	Specificity
Low grade cancer	14					85.72%	
Grade I	00	00	00	00	00	00%	00%
Grade II	14	12	00	00	02	85.72%	100%
High grade cancer	43					95.34%	
Grade III	00	00	00	00	00	00%	00%
Flat CIS	01	01	00	00	00	100%	100%
Invasive cancer	42	40	00	00	02	95.24%	100%
<b>Total</b>	<b>57</b>	<b>53</b>	<b>00</b>	<b>00</b>	<b>04</b>	<b>92.99%</b>	<b>100%</b>

## Discussion

Cytologic study of the urine as a diagnostic procedure was first introduced by Papanicolaou and Marshall in 1945.<sup>24</sup> Urinary tract cytology is asked as a diagnostic aid by Urologists rather than as a detection technique for urinary tract cancer.

The Urologists in nearly every instance seeks the assistance of diagnostic cytology only in those cases where a suggestion that a malignant neoplasm of the urinary tract exists<sup>25</sup> In 1961, Crabbe initiated urine cytology as a successful method for screening high risk population or industrial population.<sup>3,18</sup>

The practical value of cytological examination of urine is, first in reducing the chance of biopsy sampling error and second, in the detection of cancer in patients who refuse frequent Cystoscopy.<sup>20</sup> Urine cytology before review Cystoscopy may help in avoiding unnecessary general anaesthesia and reduce both cost and patient morbidity.<sup>26</sup> As a follow up procedure, cytology may enhance the value as well as reduce the number of cystoscopies performed by accurately indicating when a search for cancers needs to be undertaken.<sup>27</sup>

Since 50-70% of the patients with transitional cell carcinoma particularly the superficial transitional cell carcinoma will experience a recurrent tumor, it is important to have a non- invasive assay that can predict the likelihood of bladder transitional cell carcinoma recurrence.<sup>13</sup>

Though it is reported that any kind of therapy particularly intravesical instillation and radiotherapy, reduces the diagnostic accuracy of cytologic diagnosis, cytology has proven sensitive to the detection of recurrent and persistent transitional cell carcinoma following treatment with chemo therapy, radiation or surgery. In such cases the abnormal areas of epithelium in the bladder may be extremely difficult for the urologist to find by biopsy. One should not be lulled by a normal appearing bladder and negative biopsies in these cases in to believing that the cytology reports are incorrect. In the author's series, there are 17 cases for analysis following therapy by radiation, surgery, chemotherapy or a combination of these. Out of 17, there are 2 negative reports only. These recurrences have been identified cytologically prior to clinical or histological detection.<sup>14</sup>

Cytologic studies of the urinary sediment and multiple biopsies of seemingly unaffected areas of the bladder are essential in the evaluation of

patients with bladder tumors. In fact it has been shown in high risk groups and in patients with previously treated bladder lesions, that non-papillary carcinoma in-situ, may be detected by cytologic studies in the absence of marked cystoscopic abnormalities. In the majority of these patients, clinical evidence of carcinoma followed, often many years.<sup>8</sup> Several other studies, showed that malignant cells often appear in urinary samples long before cancer can be confirmed in tissues.<sup>9</sup> The most important advantage of the method is its ability to indicate the presence of a tumor at a very early stage of its development, often before any presenting symptom or other urinary abnormalities have given an indication of its presence.<sup>(2,4)</sup> Positive urine cytology findings may predate the development of discernible cancer by months to years.<sup>23</sup> Early precancerous lesion in the bladder may not be visible cystoscopically and cytology may therefore allow for an earlier diagnosis of malignancy, months to years before the cancer would be found cystoscopically.<sup>14,28</sup>

In concordance with the previously published experiences, urinary cytology is a valuable indicator, especially of urothelial changes in the cystoscopically normal looking bladder and in some cases is superior to multifocal biopsies.<sup>(10)</sup>

This study demonstrated the accuracy of cytology by evaluating comparison of cytologic and histopathological diagnoses. In the present study, results of urine cytology of 57 patients were correlated with tissue diagnosis. Cytologic diagnosis was made in symptomatic patients and 100% of the patients presented with gross or microscopic painless haematuria. Cytologic diagnosis was constantly earlier than pathologic diagnosis in this series.

Histopathological diagnoses were non invasive papillary tumors 14 (25%), carcinoma in-situ 1 (2%) and invasive carcinoma (all grades / types) 42 (74%). Out of 57 cases, cytological diagnosis was positive in 53 cases (93%) and negative in 4 cases (7%). There were no atypical or suspicious cases. Among 14 (25%) non invasive papillary transitional cell carcinoma grade II, 12 (86%) were positive cytologically. There was no grade I and

III case. One (2%) non papillary carcinoma in-situ gave 100% positive cytologic results and out of 42(68%) invasive lesions, 40(95.24%) gave positive results.

In a study of 114 patients having known bladder cancer, cytology was positive for malignant cells in 80 cases (70.2%), negative in 23 patients (20.2%) and doubtful in 11 cases (9.6%).<sup>(40)</sup> In a study by Farrow based on 10338 patients cytology was positive in 84% of 78 invasive cancers and 83.5% of 152 carcinoma in-situ. In 650 papillary tumors, cytology was abnormal in 47.4%.<sup>19</sup>

L.G. Koss made cytohistologic correlation in 203 cases and noted that only one of the six grade I papillary tumors had cancer cells in the urinary sediment. Of 64 grade II papillary tumors, 48 (70.5%) were cytologically positive. With 4 exceptions, all of the 62 grade III tumors were identified by cytology as cancerous. Cytology was also positive in 100% and 92% cases of carcinoma in-situ and invasive carcinomas respectively. Of the 103 high grade lesions (comprising grade III papillary lesions, invasive carcinomas and flat carcinoma in-situ, 97 (94%) gave positive cytologic results.<sup>27</sup> Comparison of cytohistologic correlation with previous studies also gave similar results which is in concordance with the present study. In this series there were no papilloma or grade I papillary carcinomas that is why the diagnostic accuracy. The results also points to the higher accuracy of cytologic positive cases when the lesions becomes high grade and particularly invasive.

The potential value of urine cytology has been reduced, however by the relative inexperience of most pathologists in the examination of urinary specimens and by the lack of cellular criteria specifically reflecting the morphology of low grade papillary lesions.<sup>9,15</sup> Crabbe pointed out 11 of 57 such tumors on cytologic specimens. Koss et.al. also emphasized the low diagnostic yield of urine cytology in low grade TCC. This is because of the individual cells shed in voided urine may not be sufficiently significant for the diagnosis of cancer.<sup>18</sup>

The well differentiated tumors are not readily detected cytologically but results improve with more undifferentiated higher grade lesions.<sup>19</sup>

Most papillomas and grade I TCCs are diploid whereas most grade II and III TCCs are aneuploid.<sup>4,5</sup> Aneuploid tumors were much more likely to progress to invasion than were diploid tumors. Hence the conclusion is that cytology of voided urine may be not only of diagnostic but also of prognostic value: positive cytology presumably identifies patients at high risk. High grade lesions (grade III papillary lesion, invasive carcinomas and flat CIS) of clinical significance and principally the non papillary CIS are reflected in voided urine with a very high degree of accuracy and specificity.<sup>27</sup>

Consistent with previously published data, this study showed the highest diagnostic accuracy with high grade tumors and lowest with low grade tumors with maximum invasion limited to the lamina propria.

The percentage of false negative reports in this series can be partly due to poor sampling or low grade particularly diploid tumors not revealed in this study or due to poor techniques adopted. In a study of 91 patients, urine cytology was 75% sensitive and 94% specific.<sup>12</sup> Sensitivity of urine cytology in 860 patients with urinary tract cancer was 77% and the specificity is 97%.<sup>(15)</sup> L.G. Koss in a study of 183 cases having bladder cancer, described the sensitivity of 82.5% for all tumors. If one excludes grade-I and II tumors, the sensitivity for all high grade lesions and flat CIS.<sup>6,27</sup> In low grade cancers, the sensitivity is 66.2%, for grade-I 16.7 % and for grade--II 71.6%. The specificity was 100% since there was no false positive cases.<sup>27</sup>

In a study of 898 tumors of urinary tract, the sensitivity was 83%. Approximately 1/3rd of the well differentiated grade-I papillary carcinomas was considered negative and one third were considered abnormal or suspicious. The sensitivity increases to 80% for grade II and to 94% for grade-III TCC.<sup>3</sup> The sensitivity and specificity of the present study correlate well with other previous studies indicating further that urine cytology is a very rewarding area of diagnostic cytopathology on the part of the patients as well as for the cytopathologists.

In this study the non-invasive technique was adopted and voided urine specimen was chosen over bladder washings or barbotage as an ideal method of collection of urine. The purpose of this is to see how a simplest test can be helpful in diagnosing malignant tumors of urinary bladder.

Urine cytology is not a popular method for screening or detection of malignancy in the urinary tract in our country. The finding of malignant cells in urine is highly suggestive of the presence of cancer arising from transitional epithelium.<sup>24</sup> Urine cytology has immense value as a non-invasive technique, not only as a diagnostic tool but also as a prognostic factor. Positive cytology correlates well with grade, stage and prognosis of bladder tumors, so it can be used in the detection, diagnosis and follow-up of the primary tumor and for recurrent tumors receiving therapy. Urine is a very inhospitable fluid for cells but the basis for deleterious effects is not known. Quick removal of the fluid portion of urine and prompt fixation of the freshly desquamated cells is the main reasons for improved presentation.<sup>22</sup>

One comment about false negative, which applies to any fluid in which cells are suspended, is that collectors must be trained to pour a sample immediately or shake the container if the fluid has stood for a while (say 15 minutes) and the cells have settled, thus the specimen collected gets its share of the cells.<sup>25</sup> False negative cytology in low grade lesions is therefore not unexpected. False positive diagnoses are probably not important. A positive cytological diagnosis of bladder cancer does not lead directly to cystectomy or other radical therapy.<sup>22</sup> An early therapeutic decision for total cystectomy may be justified in patients in whom diffuse abnormality of bladder epithelium, is documented by cytologic studies and multiple biopsies.<sup>8</sup>

Even after cystoscopy and transurethral resection of bladder tumor (TURBT), urine cytology has prognostic value/importance. If urine cytology shows high grade cancer cells and tissue diagnosis after removal, reveals a low grade tumor, then the conclusion will be that besides the low grade cancer, there might be high grade abnormality within the bladder not detected during Cystoscopic removal. So the out come of patients will differ in such cases. A tumor localized within a

diverticulum or higher up in the tract, may escape detection during cystoscopy but urine cytology can give a meaningful diagnosis in such cases, if the tumor is of high grade which was a false positive diagnosis on the clinician's point of view. This possibility should be kept in mind and a thorough search should be made to detect the lesions.

As urine cytology have the advantage of sampling whole bladder mucosa, invasive diseases or flat CIS can be predicted long before identification by USG or cystoscopy, thus helps in increasing survival of the patients.

The criteria of diagnosing low grade cancers of bladder (papilloma, TCC grade-I) should be refined more for further sophistication since false negative results are inherent with these tumors, thus decreasing the overall sensitivity of the tool used. The cytologist should also be aware of the technique about preparation of smears from voided urine since it differs significantly from FNA or other exfoliative cytology smear preparation because of the high fluidity, less number of cells and less protein in the urine.

## **Conclusion**

A more or less definitive pre-operative diagnosis of malignant tumors of urinary bladder can help the Urologists for making decision about the plan of surgery or of radiotherapy or chemotherapy. The out come of the therapy instituted can also be assessed through cytology. There are several methods of making a pre-operative diagnosis. Among all of the invasive and non-invasive technique, voided urine cytology is one of the important non invasive methods which can give results very closer to the histologic diagnosis or at least can say about the nature of the tumors if the cellular yield is high.

Voided urine cytology, purely a non-invasive technique, can be done as a first line cost effective method, in adjunct to other investigations. In a developing country like Bangladesh where facility for cystoscopy and relevant investigations are not available practically in most of the institutions and particularly in the rural or remote areas, urine cytology can prove to be a simple non-invasive valuable tool in the detection, diagnosis and follow up of primary and recurrent urinary bladder tumors.

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All correspondence to:  
S M Badruddoza  
Professor  
Department of Pathology  
Rajshahi Medical College Rajshahi