

CLINICAL, HISTOLOGICAL AND CYTOLOGICAL STUDY OF UROTHELIAL NEOPLASMS OF URINARY BLADDER

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Abstract

Background: Urinary bladder neoplasm is the second most prevalent malignant tumor of the urinary tract causing approximately 3% of cancer deaths. Recently it has been reported that clinical and cytological examination of urinary fluid can detect cancer, especially in patients with haematuria. Hence, the present study was carried out to determine the effectiveness of the urinary bladder's clinical, histological and cytological parameters to diagnose urinary bladder neoplasm. **Materials and Methods:** A present descriptive study was carried out at the Dept. of Pathology from December 2012 to May 2014. Total of 68 patients with urothelial neoplasms of the bladder was enrolled for the study. The clinical, cytological and histological data of all participating patients were collected and evaluated statistically using SPSS software version 21. **Result:** The majority of the patients in the present study are male (89.7%) and belong to the age group of 61 to 70 years (36.8%). 66.2% of patients were smokers, whereas 41.18% of patients were observed with irritation symptoms. Urine cytology revealed that 26.5% of cases showed malignant cells. The grading of urinary malignancy showed that 38.2% cases were high grade, 60.3% cases were low grade, whereas 1.5% cases were reported with low malignant potential. All the histological parameters showed an excellent correlation in the grading of urothelial neoplasia. **Conclusion:** The results from the present study conclude that clinical, cytological and histological parameters could be a good screening for detecting urothelial neoplasm.

INTRODUCTION

Urinary bladder cancer is the fourth most common non-skin cancer in men and the ninth most common cancer in women in the United States.^[1] In the United States, an estimated 61,420 new cases of bladder cancer were detected in 2006. According to epidemiological research, tobacco smoking has been linked to 50 percent of bladder cancer incidences in males and 30 percent in women. Another 25% of these cancers in males and 11% in women are caused by various chemical and industrial exposures.^[2]

The most common histological kind of bladder cancer is urothelial (transitional cell) carcinoma. The recurrence, progression, and patient survival rates of urothelial carcinoma are closely associated with tumour grade and stage.^[3] The tumor stage is defined by invasiveness and metastasis, whereas

cytological features determine tumour grade. Stage Ta denotes non-invasive papillary urothelial carcinoma, while stages T1, T2, T3, and T4 denote invasion into sub-epithelial connective tissue, muscle, perivesical tissue, and neighbouring organs, respectively.^[4]

Approximately 75% of newly diagnosed urothelial neoplasms of the bladder are non-invasive. Every year, approximately 1,10,500 men and 70,000 women are diagnosed with new cases and 38,200 patients in the European Union and 17,000 US patients die due to this neoplasm.^[5] Among the risk factors Smoking accounts for approximately half of all urothelial neoplasm of the bladder; others are occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons^{1,2} etc.

Grading of urothelial neoplasm is not of much significance in the case of invasive tumors. Invasion indicates aggressive treatment. In the non-invasive

type, urothelial neoplasm prognosis depends on the cytological grade of the tumor. Nowadays, the cytopathological examination of urine or other fluid samples from the urinary tract is a routine non-invasive diagnostic procedure to detect urinary tract cancer, foremost bladder cancer, especially in patients with painless haematuria.^[6,7] This study is to relate clinical, histological and cytological aspects of the urothelial neoplasm of the bladder.

MATERIALS AND METHODS

This prospective observational study was conducted in the department of pathology in all histopathologically positive Urothelial neoplasm of the bladder was included in the study from December 2012 to May 2014. Inclusion criteria: Patients investigated for bladder neoplasm, for which histopathological examination done included in the study. Exclusion criteria: Those cases, which were not proved histopathologically to be urothelial neoplasm of the bladder, were excluded. In addition, those patients who were previously diagnosed to have urothelial neoplasm of the bladder were excluded.

A total of 68 patients with urothelial neoplasms of the bladder were studied. Statistical analysis was done by frequency measurements and cross-tabulation using SPSS software version 21.

Urine cytology: Preoperatively, urine cytology was done in all cases with clinical features suspicious of urothelial neoplasm of the bladder (All the histopathologically proven cases of urothelial neoplasms took for the study).

10 ml of voided urine was centrifuged within four hours and made thin smears from the sediments. Both wet and dry smears were made on glass slides. Wet smears were immediately fixed in 85 % isopropyl alcohol and stained with conventional Papanicolaou (Pap), dry smears were air-dried and stained with Giemsa. The entire stained smear in the slides was examined under dry high power to look for malignant cells. Slides were then reported as positive for malignant cells or negative for malignant cells.

Both cystoscopic biopsies and TURBT (Trans Urethral Resection of Bladder Tumor) specimens received in the department of Pathology were fixed in 10% formalin, processed and paraffin-embedded blocks were cut into 4-5 μ m sections and stained by Haematoxylin & Eosin (H&E)⁸. In this study, grading was done based on the WHO/ISUP grading system.^[9]

To evaluate the type of pattern, whether papillary or solid. In addition, the presence or absence of polarity, cell cohesiveness, pleomorphism, nucleoli and necrosis was recorded. The microscopic features were further evaluated for mitosis, whether frequent (Frequent mitosis->10 mitosis/ 10 hpf) or present and distribution of chromatin, whether fine or vesicular.

Based on these microscopic features, neoplasms were graded to Low grade/High grade/Low malignant potential (PUNLMP). The results of urine cytology were compared with histopathological grading.

RESULTS

In the present study of 68 participating patients, a maximum of 25 (36.8%) were observed in the age group of 61 to 70 years, followed by an age group of above 70 years 19 (27.9%) and an age group of 51 to 60 years 12 (17.6%). However, at least patients 3 (4.4%) were observed in the age group of below 40 years. Of all the 68 patients majority were reported to be male, 61 (89.7%) and only 7 (10.3%) patients were female. Upon examining the smoking history of patients, it was found that none of the female patients in the study has a history of smoking and 45 out of 61 male patients were reported with a history of smoking that corresponds to 66.2% of total patients. The clinical examination of all patients showed that 21 (41.18%) patients had irritation symptoms, whereas 40 (58.82%) did not have any irritation problems. [Table 1]

Of all patients, 18 (26.5%) patients observed malignant cells in urine cytological analysis, whereas the remaining 50 (73.5%) did not show any malignant cells.

In the present study, the grading of urinary malignant was done per WHO/ISUP 1998 grading systems. There were 26 (38.2%) patients with high-grade, 41 (60.3%) patients with low-grade urothelial neoplasia. Whereas only 1 (1.5%) patients were observed with low malignant potential [Figure 1].

All patients' histological (microscopic) observation was examined and correlated with the grading of Urothelial neoplasms. A solid pattern was found only in high-grade carcinoma and was observed in 17/26 (65.4%) cases of high-grade carcinoma. However, in the case of low-grade neoplasms, all of them showed papillary patterns (100%). Polarity was lost in all high-grade carcinomas (100%). Cell cohesiveness was lost in 12/26 (46.15%) of high-grade carcinoma, but in the case of low-grade neoplasms, cohesion was noted in all cases. Pleomorphism and nuclear chromatin were noted in all the high-grade carcinoma (100%). All the high-grade tumors showed nucleoli (100%), and none of the low grades had Nucleoli. All the high-grade carcinomas showed frequent mitosis (100%). Necrosis was noted only in the case of high-grade carcinomas and it was observed in 16/26 (61.5%) of high-grade carcinomas [Table 2].

Association of Urine cytology for malignant cells with grading was evaluated in all patients. It was observed that out of 26 cases of high-grade carcinoma, 12/26 (46.2%) showed malignant cells in the urine, but out of 42 low-grade neoplasms, only 6/42 (14.3%) showed malignant cells in the urine, and this was statistically significant ($p=0.004$). The

detection rate of malignant cells in urine was higher in higher grades compared to lower grade neoplasms

[Figure 2].

Table 1: Distribution of patients characteristics

Patient characteristics		Frequency	Percentage
Age group	<40	3	4.4%
	41-50	9	13.2%
	51-60	12	17.6%
	61-70	25	36.8%
	>71	19	27.9%
Gender	Female	7	10.3%
	Male	61	89.7%
Smoking history	Smoker	45	66.2%
	Non-smoker	23	33.8%
Clinical presentation	Hematuria	68	100.0%
	Irritation	28	41.2%

Table 2: Correlation of histological parameters with Grading of Urothelial neoplasms

Histological parameters		High grade	Low grade
Pattern	Papillary	9	42
	Solid	17	0
Polarity	Lost	26	0
	Present	0	42
Cohesiveness	Lost	12	0
	Present	14	42
Pleomorphism	Absent	0	42
	Present	26	0
Nuclear chromatin	Hyperchromatin and vesicular	26	0
	Fine	0	42
Nucleoli	Absent	0	42
	Present	26	0
Mitosis	Frequent	26	0
	Present	0	42
Necrosis	Absent	10	42
	Present	16	0

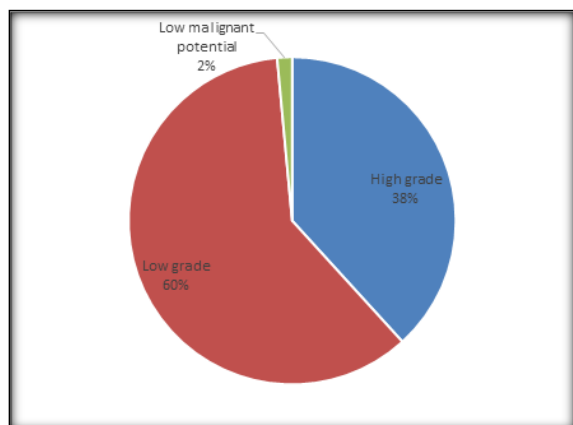


Figure 1: Grading of urothelial neoplasm

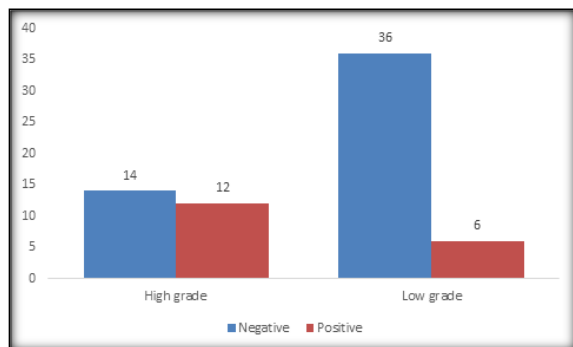


Figure 2: Association of urine cytology for malignant cell with grading (n=68)

DISCUSSION

Urothelial carcinoma of the bladder is the second most frequent malignancy of the genitourinary tract and the third most common cause of death among people with genitourinary tumors.^[10]

According to Howlader et al,^[11] the median age at the time of diagnosis of bladder cancer is 69 years in men and 71 years in women. In addition, the textbook of Sternberg's Diagnostic Surgical Pathology mentioned that the most common age group is the 6th-7th decade of life. In the present study, most cases belonged to 61-70 years at the time of presentation, accounting for 36.8% of the total cases.^[2,3] This compared well with a study conducted by Laishram RS et al,^[12] which showed 38.5%. In our study, 82.35% patients were older than 50 years of age at the time of presentation, and this was similar to the study conducted by Al-Bazzaz,^[13] which showed that 80.6% of patients were older than 50 years at the time of presentation.

In the present study, all the cases below 40 years (3/68(4.4%)) were low-grade neoplasms. According to Wan, younger patients frequently present with lower grade neoplasms than their elder counterparts. It has also been reported that urothelial neoplasms in children and young adults appear to be biologically distinct and lack genetic instability.^[14,15]

According to Sternberg's diagnostic Surgical Pathology male: female ratio was 3-4:1.^[16] In our study, 61/68 (89.7%) cases were males and 7/68 (10.3%) cases were females with a male: female ratio of 8.7:1. According to Yavari P et al,^[17] the male- female ratio in different parts of the world is variable, and this ratio is less than three in India, Thailand and United States black. According to the present study, frequency in India is 2- 3 times more than what is documented in the literature. This disparity would be because the present study was not a population-based study.

Out of total of 68 cases, 45 patients (66.2 %) had a history of smoking. According to Zeegers MP et al,^[18] smoking is associated with more than half of bladder cancer cases in men and one-third of cases in women. In our present study, 45/61 (73.77%) had a history of smoking among the total male patients, while none of the females had.

A study conducted by Matalka I et al,^[19] showed hematuria in (69%) patients. However, in the present study, hematuria was present in all the patients (100%). This disparity might indicate that our patients seek medical help late and only when they have concerning symptoms like hematuria.

According to Farrow GM et al,^[20] 25% of patients with bladder cancer presented with irritative voiding symptoms like urgency, frequency, and dysuria. In our study, it was found to be 41.18%.

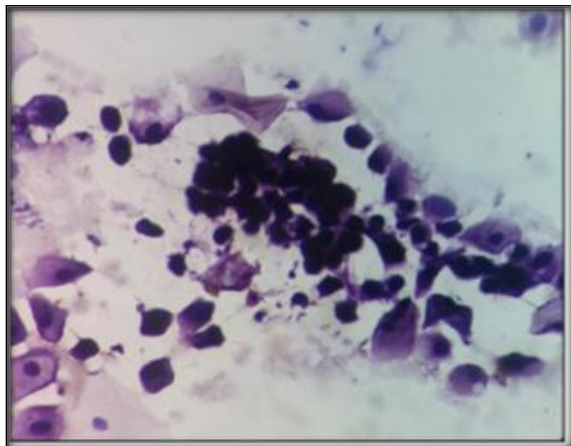


Figure 3: Voided urine cytology showing malignant cell – High-grade Type

Out of 68 cases, 18 (26.5%) cases showed malignant cells in voided urine cytology. Out of these, 12/18 (66.67%) were high-grade carcinomas, and the rest 6/18 (33.33%) were low-grade neoplasms (Low-grade neoplasm= both low-grade carcinoma and papillary urothelial neoplasm of low malignant potential). In our study, urine cytology detected more cases of high-grade neoplasms [Figure 3], i.e. 46.8 % (12 out of 26 cases of high-grade carcinoma) compared to low-grade neoplasms, where the detection rate was low -14.3% (6 out of 42 cases). A study by S Pedamallu,^[21] showed High-grade neoplasms (82.5%) were more likely to have positive malignant cytology than low-grade

neoplasms (13%). The detection rate of low-grade neoplasms by urine cytology in our study was comparable with that of S Pedamallu,^[21] where the detection rate was reduced in the case of high-grade neoplasms. This superior detection rate of high-grade neoplasms by voided urine cytology is significant (P value=0.004) in our study compared to low-grade neoplasm where detection rates are poor.

Urothelial neoplasms were classified according to the scheme proposed by the WHO/ISUP. In addition, pattern, polarity, cell cohesiveness, nuclear pleomorphism, nuclear chromatin, nucleoli, mitosis and necrosis, were assessed for grading of these tumors.

In our study, the majority of the patients, that is, 41/68 cases (60.3%), presented with low-grade carcinoma [Figure 4a], and 26/68 cases (38.2%) presented with high-grade carcinoma [Figure 4b]. Only one patient, 1/68 (1.5%), presented with papillary urothelial neoplasm of low malignant potential [Figure 5]. This data is similar to a study by Matalka et al,^[19] which showed 60% of low grade and 40% of high-grade neoplasms.

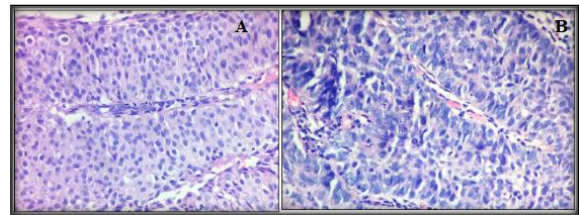


Figure 4: Urothelial carcinoma (a) Low grade papillary (b) High grade papillary

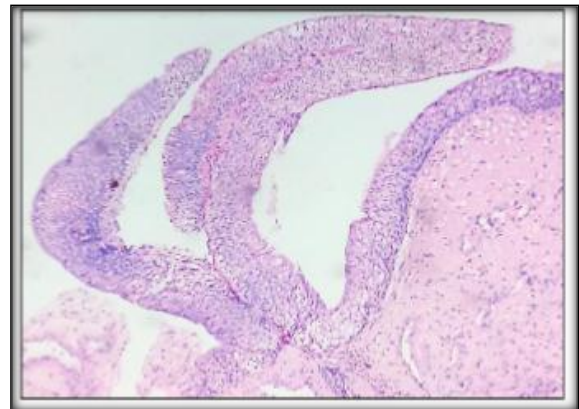


Figure 5: Papillary urothelial neoplasm of low malignant potential

In the present study, microscopic features like pattern, polarity, cell cohesiveness, pleomorphism, nuclear chromatin, nucleoli, mitosis and necrosis showed excellent relation with neoplasm grading.

A solid pattern was observed in 17/26(65.4%) of high-grade neoplasms, and 9/26 (34.6%) high-grade cases also showed a papillary pattern. 100% of Low-grade neoplasms (42/42) showed a papillary pattern. Polarity was lost in all cases of high-grade neoplasms (100%), but all low-grade neoplasms

showed polarity. Cell cohesiveness was lost in 46.15% (12/26) of high-grade neoplasms, but all cases of low-grade neoplasms retained cell cohesiveness. Pleomorphism was noted in all high-grade neoplasms (100%) and was absent in all low-grade neoplasms. Nuclear chromatin-Hyperchromatic and vesicular nucleus were seen only in high-grade neoplasms (100%). All low-grade neoplasms showed fine nuclear chromatin. Nucleoli were noted in all the high-grade neoplasms (100%). None of the low-grade neoplasms showed nucleoli. Frequent mitosis [Figure 6a] was observed in 100% of high-grade neoplasms. In the case of low-grade neoplasms, mitosis was not frequent. Necrosis [Figure 6b] was observed only in high-grade neoplasms and it was present in 16/26 (61.5%) among high-grade neoplasms.

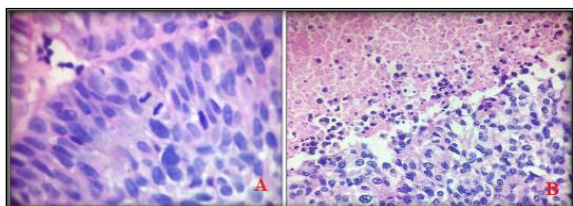


Figure 6: High-grade urothelial carcinoma (a) showing mitosis (b) with necrosis

Microscopic parameters like pattern, polarity, cell cohesiveness, pleomorphism, nuclear chromatin, nucleoli, mitoses and necrosis have been found to have a high percentage of correlation in grading and these can serve as a base model for an objective scoring system. In addition, urine cytology and symptoms like hematuria can be combined with the microscopic parameters above to develop a relevant scoring system for objective prognostication of urothelial neoplasms of the urinary bladder.

CONCLUSION

Voided urine cytology is a good screening procedure for detecting urothelial neoplasms of the urinary bladder. All patients presenting with hematuria should be subjected to urine cytology. Urine cytology is a useful modality where new tests are unavailable. The role of urine cytology is highest in the diagnosis of high-grade neoplasms. Microscopic parameters like pattern, polarity, Cell cohesiveness, pleomorphism, nuclear chromatin, nucleoli, mitosis and necrosis showed an excellent correlation in the grading of urothelial neoplasia. Urothelial neoplasm of the bladder most frequently noted in elderly age group. There is a high incidence of bladder carcinoma in males compared to females in our hospital-based study.

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