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Original Research Article

Histopathological Spectrum of Urinary Bladder Lesions With Focus on Neoplastic Lesions

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Abstract

Introduction: Lesions of urinary bladder constitute an important source of clinical signs and symptoms. Both neoplastic and non-neoplastic lesions do occur commonly, however the former being the most common type. Majority of urinary tract tumors are epithelial in origin, among which 90% of them are urothelial in origin. *Objective:* To evaluate the histopathological spectrum of urinary bladder lesions with emphasis on the neoplastic lesions with reference to 2016 WHO classification of tumors of urinary system. *Materials and Methods:* This was a prospective study and includes all the urinary bladder specimens received. They were examined grossly and processed completely as per the standard procedure. Multiple sections of 3–5 microns were taken and stained with H & E, followed by light microscopic examination to study various non-neoplastic and neoplastic lesions. *Results:* Total 65 cases were studied, 30 were cystoscopic biopsies and 35 were TURBT specimens. There were 40 males and 25 females constituting up to 61.54% and 38.46% respectively. Chronic non-specific cystitis was the common non-neoplastic lesion. Among neoplastic lesion, Invasive urothelial carcinoma was the predominant lesion constituting 22 cases (62.86%). These neoplastic lesions were more common among males (74.28%) with M:F ratio of 2.8:1. *Conclusion:* Urinary bladder lesions are most frequently encountered by surgical pathologists and are heterogenous. Both benign and malignant lesions are well documented but latter being more common. Many of these are more common in elderly people with male predilection and are often associated with smoking. Identifying the extent of invasion by microscopic examination constitutes an important aspect in urothelial carcinomas.

Keywords: Urinary bladder; Cystoscopic biopsy; Transurethral resection of bladder tumor; Invasive urothelial carcinoma.

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Introduction

Lesions of urinary bladder constitute an important source of clinical signs and symptoms.[1] Both neoplastic and non-neoplastic lesions do occur commonly, however the former being the most common type. Cystitis, malakoplakia, urachal lesions and tuberculosis are the common non neoplastic lesions encountered.[2] Cystitis is the most common inflammatory condition of urinary bladder and can presents as both acute and chronic forms. It is further classified into various types depending upon the cause, duration and histological appearance.[1,3]

Neoplastic lesions are associated with considerable morbidity and mortality throughout the world.[4] Both benign and malignant lesions do occur, however the latter being more common. Majority of urinary tract tumors are epithelial in origin, among which 90% of them are urothelial in origin.[3,4] There is a steady increase in the incidence rate of these cancers over last 60–70 years.[5] Urothelial carcinomas are also seen at other sites such as renal pelvis, ureters, urethra in the decreasing order of frequency only next to urinary bladder.[6]

Cancers of the urinary bladder are the 9thmost common cancers worldwide and second most common malignancy known to occur in genitourinary tract after prostate cancer. The incidence of bladder neoplasms is 6% and 2% in the men and women respectively. Most cases present after 5th decade.[4]

According to global cancer statistics 2012 data, approximately 4.29 million new cases of bladder cancer and 1.65 million deaths due bladder cancer has been registered worldwide. It is more common in males constituting 75% of the total burden of the disease.[7] According to Indian Cancer Registry data, it is the ninth most common cancer accounting to 3.9% of all cancers. Both benign and malignant lesions are well documented carrying significant morbidity and mortality. These malignancy manifest with complex and heterogenous signs and symptoms with a wide histopathological spectrum thus posing problem to urologists and pathologists.[3]

Urinary bladder tumors are more common in men than in women with a ratio of 3-5:1 and in urban than in rural people. The prevalence of bladder tumors is six times more common in developed countries than in developing countries.[6,8] Around 80% of the people fall in the age group of 50–80 years.[1]

Bladder cancers are not familial with rare exceptions.[1] There is well established association between some of the etiological agent in pathogenesis of bladder cancers. They can be either genetic abnormality or external agents like cigarette smoking, occupational exposure to carcinogens from chemical industry, Schistosoma hematobium infection in endemic areas, use of artificial sweeteners, patients on long term use of cyclophosphamide and analgesics and patients receiving radiation therapy for uterine cancers.[1,9,10]

Genetic factors such as null GSTM-1 (Glutathione-S transferase) and slow NAT-2 (N-acetyltransferase) polymorphism increases the risk of bladder cancer.[5] Many tumor suppressor genes and oncogenes role has been established in invasive urothelial carcinoma. These include mutations of TP53, FGFR3, PIK3CA, RB1 and HRAS with TP53 and FGFR3 together with promoter mutations of TERT.[11]

Gross and microscopic hematuria constitutes the main symptoms in many of the bladder neoplasms. Painless hematuria is the most common complaint often seen in 85% of patients with bladder cancers. This is followed by clotting resulting in painful micturition. Patients with advanced disease may present with palpable suprapubic mass or edema of lower limbs. In cases of metastasis, weight loss with abdominal or bone pain is often noticed.[12]

Cystoscopy is the endoscopic technique which is used to visualize the urethra and bladder mucosa and ureteral orifice. It is the gold standard and primary diagnostic tool in cancer detection which allows complete visualization of bladder mucosa followed by biopsy of suspicious areas for submitting to histopathological examination.[3,5]

Transurethral resection of bladder tumors (TURBT) is a therapeutic and diagnostic procedure which is used for evaluation of various clinical prognostic factors, tumor differentiation, depth of infiltration and complete removal of non-invasive papillary tumors of bladder.[4]

Materials and Methods

This was a prospective study was carried out in the histopathology laboratory of Department of Pathology in collaboration with Department of Urology, BLDEU's Shri BM Patil Medical College, Hospital and Research Centre, Vijayapura. It includes 65 cases of cystoscopic biopsies and TURBT specimens which were received in the histopathological department of Pathology from January 2016 to December 2017.

The specimen were received in 10% formalin. The tissue was grossly examined first and findings were noted. The entire tissue was processed in all the cases. They were processed as per standard procedure. Multiple sections of 3–5 microns thickness were obtained from the paraffin block and stained with H & E.

Histopathological examination of cystoscopic bladder biopsies and TURBT specimens was carried out and the lesions were classified into various non-neoplastic and neoplastic lesions on the basis of light microscopic examination.

Results

A total of 65 urinary bladder specimens were studied which included both cystoscopic bladder biopsy and TURBT. 30 cases were cystoscopic biopsies and 35 cases were TURBT specimens. In the present study, the age group ranged from 2years to 80 years. There was clustering of cases between 51–80 years of age with maximum cases noted in 61–80 years constituting up to 52.08% of the entire samples among the study. There were 40 males and 25 females constituting up to 61.54% and 38.46% respectively. The present included 30 cases (46.15%) of non-neoplastic lesions and 35 cases (53.85%) of neoplastic lesions.

Among the non-neoplastic lesions (Fig. 1), chronic nonspecific cystitis was the predominant type constituting up to 66.67% of all cases. Other types of cystitis received were three cases of acute on chronic cystitis, one case each of granulomatous cystitis, polypoidal cystitis, eosinophilic and follicular cystitis. The variants of normal histology included in the study were one case each of cystitis cystica, cystitis glandularis and one case of fibroepithelial polyp which was present in a 2 year boy.

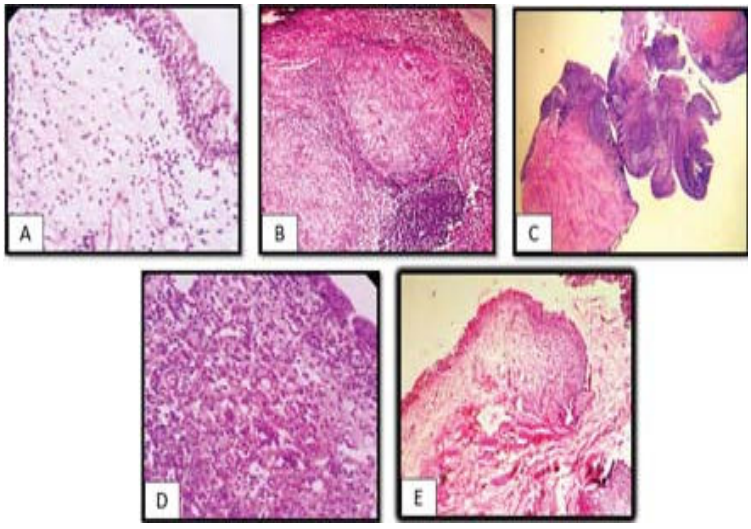

Fig. 1: Various forms of cystitis. A) Chronic non-specific cystitis, B) Granulomatous cystitis, C) Follicular cystitis, D) Eosinophilic cystitis and E) Polypoidal cystitis.

Among the neoplastic lesions, the present study showed a significant increase in the number of cases in the age group of 61 to 80 years together constituting 57.14% with nil cases observed in upto the age of 40 years. There were 26 males and 9 were females with M:F ratio of 2.8:1 for the neoplastic lesions in the present study.

Among the neoplastic lesions (Table 1), invasive urothelial carcinoma (IUC) was found to be predominant type constituting 22 cases (62.86%), followed by 4 cases (11.43%) of Papillary urothelial neoplasm of low malignant potential, 6 cases (17.14%) of non-invasive papillary urothelial carcinoma, low grade, 2 cases (5.71%) of non-invasive papillary urothelial carcinoma, high grade and one case (2.86%) of urothelial carcinoma in situ (CIS). Depending upon the microscopic extent of the lesions, 13 were non-invasive papillary neoplasms, 9 were invasive papillary carcinoma with extent upto lamina propria (superficially invasive carcinoma, T1), 13 cases were invasive papillary carcinoma with extent upto muscularis propria.

Table 1: Showing distribution of various urothelial neoplasms in comparison with other studies

Studies	Shah PY et al.[56]	Shruti HP et al.[4]	Laishram et al.[60]	Present study
Papilloma	0	2 (4%)	2 (4.44%)	0
Urothelial carcinoma in situ	0	0	0	1 (2.86%)
Papillary urothelial neoplasm of low malignant potential	3(15.79%)	3 (6.12%)	1 (2.22%)	4 (11.43%)
Non-invasive papillary urothelial carcinoma, Low grade	6(31.58%)	17 (34.6%)	14 (31.11%)	6 (17.14%)
Non-invasive papillary urothelial carcinoma, High grade	1(5.26%)	14 (28.5%)	9 (20%)	2 (5.71%)
Invasive urothelial carcinoma	9(47.37%)	13 (26.5%)	19 (42.22%)	22 (62.86%)
Total	19	49	45	35

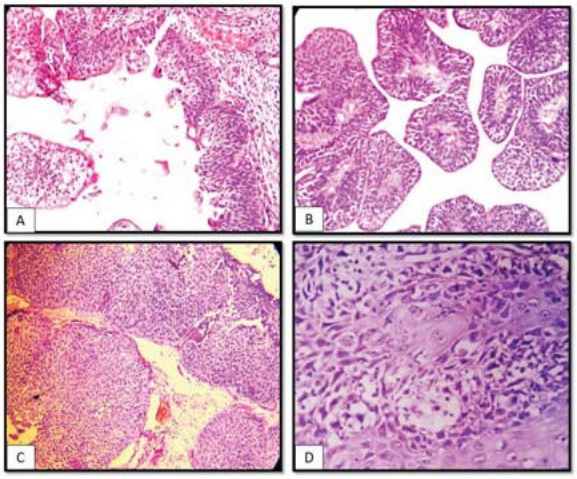

Fig. 2: Various neoplastic lesions- urinary bladder. A) Papillary urothelial neoplasm of low malignant potential [H&E, 100x], B) Non-invasive papillary urothelial carcinoma, low grade [H&E, 100x], C) Non-invasive papillary urothelial carcinoma, high grade [H&E, 100x,400x], D) IUC-squamous differentiation [H&E, 400x].

Discussion

Diseases of the urinary bladder constitute an important source of clinical signs and symptoms, these are more disabling than lethal.[1] Both neoplastic and non-neoplastic lesions collectively accounts for notably high amount of morbidity and mortality.[3] Cystoscopy, which is a gold standard, primary diagnostic tool and TURBT being the most commonly practiced therapeutic and diagnostic procedure allows urologists to completely visualize bladder mucosa followed by sampling of the tissue for the histopathological examination.[3,13]

The present study included 65 cases, 30 were cystoscopic biopsy and 35 were TURBT. Out of 30 non-neoplastic lesions were predominantly composed of chronic non-specific cystitis (20 cases), remaining 10 cases were composed of inflammatory lesions like acute on chronic cystitis, granulomatous cystitis, polypoidal cystitis, eosinophilic cystitis, follicular cystitis, fibroepithelial polyp and metaplastic lesions like cystitis cystica and cystitis glandularis. These observations were similar to study done by Shruti et al.[3] and Srikoustubah et al.[14]

Among the neoplastic lesions studied, majority of them were originating from the lining urothelial cells. Out of which both non-invasive and invasive lesions were observed to occur predominantly in males accounting to 26 cases (74.29%), remaining 9 cases were females (25.71%) with a Male: Female ratio of 2.8:1. Various studies highlighted the association bladder neoplasms and increased male susceptibility which was in concordance with the present study. However, there is wide range of M:F ratio observed between various studies ranging from lowest being observed is 2.29:1 in study by Shah et al.[15] to highest observed in study by Srikoustubah et al.[14] having M:F ratio of 5.25:1. This variation could be attributed to the various environmental factors taking part in the evolution of the neoplastic lesions.

IUC was predominant type among the urothelial neoplasms constituting around 62.86% of all neoplastic lesions in the present study which was more than in studies done by Shah et al.[15] and Laishram et al.[16] However, they also reported IUC as the predominant histological type of urothelial carcinoma.

As in 2004, the new 2016 classification continues to recommend the use of 1997 ISUP system for grading of the tumors. They have remarkable propensity for divergent differentiation. However, data is limited to establish the outcome of patients depending on the degree of divergent differentiation. For defining IUC with divergent differentiation, the tumor should be arising from urothelium of the urinary tract containing the usual morphology of the urothelial carcinoma along with some percentage of other morphologic entities like squamoid, glandular, small cell and trophoblastic differentiation.[11]

IUC with any differentiation was the predominant type observed among the invasive carcinoma in the present study which was in concordance with the other studies like Goyal et al[2] and Shruti et al[3]. Apart from this, cases like IUC with squamous differentiation, glandular differentiation, clear cell differentiation and sarcomatoid differentiation of IUC which was similar to other studies (Table 2, Fig. 3).

Table 2: Showing various differentiations among invasive urothelial carcinoma in comparison with other studies.

Differentiation	Goyal VK et al.[2]	Shruti HP et al.[4]	Present study
Nil	82 (92.13%)	13 (86.67%)	13 (76.48%)
Squamous	5 (5.61)	1 (6.67%)	1 (5.88%)
Glandular	1 (1.12%)	0	1 (5.88%)
Nested	1 (1.12%)	0	0
Clear cell	0	0	1 (5.88%)
Sarcomatoid	0	1 (6.67%)	1 (5.88%)

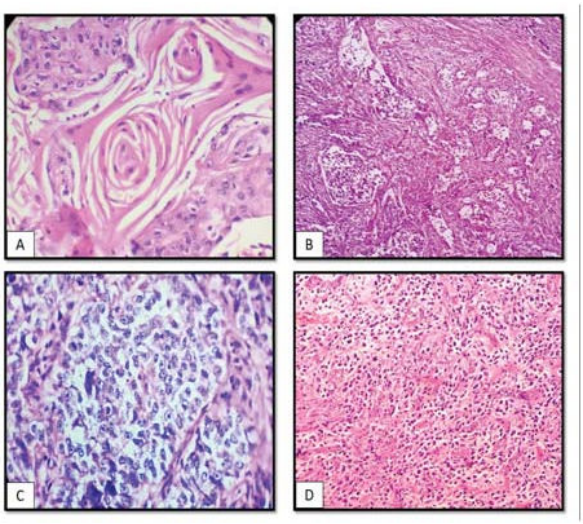

Fig. 3: Various forms IUC with differentiation, A) IUC with squamous differentiation – keratin pearl formation [H&E, 400x], B) IUC- glandular differentiation [H&E, 100x], C) IUC- Clear cell variant [H&E, 400x], D) IUC-Sarcomatoid variant [H&E, 400x].

The most important aspect during microscopic evaluation of these urothelial carcinomas is identification of invasion and commenting on the extent of invasion. This is characterized by presence of nests, clusters or singly scattered tumor cells in the lamina propria or muscularis propria. The evidence of invasion is further supported by presence of desmoplastic response and tumor cells within retraction spaces.[12] The sampling of muscularis propria is very important to confirm its

involvement by tumor or not. Repeat biopsies from the early invasive tumors (T1) will help to provide appropriate staging and assessment of tumor progression.[17] Regional lymph node sampling and staging has a significant role in prognostication. It is demonstrated that the outcome is good with metastatic disease to lymph node than the metastasis to other viscera and bone.[17]

The fourth edition (2016) of WHO classification of tumors of urothelial tract replaced the old term papillary urothelial hyperplasia and introduced the term urothelial proliferation of uncertain malignant potential. It is characterized by thickening in the lining urothelium with minimal or no cytological atypia. The undifferentiated variant of IUC of 2004 classification has been renamed as "poorly differentiated" variant in 2016 classification. Among the glandular neoplasms, signet ring cell and clear cell variants of adenocarcinoma from these glandular neoplasms group and added them in IUC.[11]

To conclude, Urinary bladder lesions are most frequently encountered by surgical pathologists and are heterogenous. Both benign and malignant lesions are well documented but latter being more common. Many of these are more common in elderly people with male predilection and are often associated with smoking. Identifying the extent of invasion by microscopic examination constitutes an important aspect in urothelial carcinomas. Invasion of muscularis mucosa and muscularis propria has to be differentiated carefully as the prognostic and therapeutic aspects are entirely different in both of them. In cases of dilemma IHC is most helpful. Awareness regarding the various histological features of these lesions, their neoplastic potential, risk of recurrence and possible pitfalls helps for accurate diagnosis.

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