Original Research Article

Indian Journal of Pathology: Research and Practice
Volume 6 Number 4, October - December 2017 (Part-II)
DOI: http://dx.doi.org/10.21088/ijprp.2278.148X.6417.42

Spectrum of Urothelial Lesions at a Tertiary Care Centre

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Abstract

Introduction: Bladder cancer is the 7thmost common cancer worldwide and constitutes for 90% of all primary tumors of the same. The current study was undertaken to study the histopathological lesions of the bladder and to determine the association of age and sex, histopathological variants and tumor grading and staging. *Objectives:* To study the histomorphological patterns of various lesions in bladder biopsies and to analyze the frequency of different urothelial lesions. *Methods:* The study was conducted from June 2015 to July 2017, in department of Pathology, at DY Patil Medical College, DPU, Pimpri, Pune. Related clinical history of all the cases was recorded. *Results:* Total of 73 bladder biopsies were analyzed. Clinical symptoms of hematuria, abdominal pain and an increased frequency of micturition were the usual presenting symptoms. Male dominance was noted as compared to females with M: F ratio of 2:1. Maximum incidences of cases were noted in the age group of 61 to 80 years.Neoplastic lesions comprised a total of 74.28% in contrast, the benign lesions were 27.3%. Amongst the malignant lesions majority were of urothelial carcinoma (54.7%) followed by papillary urothelial neoplasm of low malignant potential, low grade papillary urothelial carcinoma and sarcomatoid urothelial carcinoma (2.7%) and urothelial dysplasia (8.21%). *Conclusion:* Neoplastic lesions were more common than non- neoplastic, most common being urothelial carcinoma and their histopathological variants. Significant male predominance was noted with hematuria being the most common presenting symptom and advanced age had an overall poor survival rate. Pathological grading plays a key role in the prognosis of these tumors.

Keywords: Urothelial Lesions; Hematuria; Urothelial Carcinoma; Histological Variants.

Introduction

Diseases of urinary bladder, neoplastic and non-neoplastic are common and have significant morbidity and mortality associated. The non-neoplastic lesions comprise of malakoplakia, urachal lesions, cystitis, and tuberculosis. Urothelial carcinoma comprises of 90% of all the bladder tumors and is the 9th most common canceraccounting for 3.9% of all tumors according to Indian Cancer Registry Datait is the seventh most common cancer with an estimated global incidence of 3,30,380 new cases in 2012 [1,2]. The incidence of bladder carcinoma is higher in men than in women, more in developed than in developing nations and higher in urban population than rural with 80% of patients presenting between 50 and 80 years. In majority of bladder cancers which are newly diagnosed about 75 -80 % are superficial, non-invasive papillary urothelial carcinoma, amongst which nearly 75% patients show recurrence over time, and this has only bought focus on bladder cancer as the second most common amongst males after prostate carcinoma [3]. Most frequent presentations being gross and microscopic hematuria. The associated risk factors being environmental factors, industrial exposure specially aryl amines, prolonged usage of analgesics, cigarette smoking and Schistosoma hematobium infestations [4]. Lesions from the bladder have heterogeneous presentations with variable morphological and behavioral pattern [5]. Remarkable progress has been made in the noninvasive methods specially imaging techniques like cystoscopy, in which scientist continue to identify potential markers and

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(Received on 09.09.2017, **Accepted on** 25.09.2017)

surrogate end points for physical examination of bladder lesions. Cystoscopy is instrumental in diagnosing bladder tumors, which allows direct view of the bladder mucosa and biopsies from suspected sites. With this histopathological examination of the biopsy material remains the prime tool for diagnosing the lesions. The aim of the current study was to study the histomorphological patterns of various lesions in bladder biopsies and to analyze the frequency of different urothelial lesions in a tertiary care center.

Materials and Methods

The study undertaken, included both retrospective and prospective cases from June 2015 to July 2017, in department of Pathology, at DY Patil Medical College, DPU, Pimpri Pune, and all the cases with bladder lesions attending the urology department and those who underwent biopsies were included. The biopsies taken were fixed in 10% formalin. The histopathological processing of the samples was done according to the protocol and stained with Hematoxylin and eosin. The cytochemical stains were utilized where so ever needed. The bladder lesions were studied according to the WHO/ISUP 2004 classification. The exclusion criteria consisted of inadequate biopsies and autolyzed samples.

Results

Total of 73 bladder biopsies were analyzed during the period of study. The patients presented with the usual clinical symptoms of hematuria, abdominal pain and an increased frequency of micturition (Table 1). Male dominance was noted as compared to females comprising of 64.3% and 35.6% respectively. Male to female ratio of 2:1 (Table 2). The malignant lesions with 52% (38cases) were seen more in men than in women and was 21.9% (16 cases) (Table 3). The age of the study group ranged from 10 years to 80years and maximum incidence of cases were noted in the age group of 61 to 80 years.

Varied range of lesions were noted in the study which have been tabulated (Table 4). The neoplastic lesions comprised a total of 74.28% in contrast the benign lesions which were 27.3%. The lesions were histologically graded according to the WHO/ ISUP (2004). The highest incidence amongst the malignant lesions was that of urothelial carcinoma (54.7%) followed by papillary urothelial neoplasm of low malignant potential, low grade papillary urothelial carcinoma and sarcomatoid urothelial carcinoma (2.7%) and urothelial dysplasia (8.21%). The benign lesions comprised of eosinophilic cystitis (6.8%), followed by chronic cystitis and cystitis cystica (5.4%) and others like follicular and hemorrhagic cystitis. As per the TNM staging, majority of tumors were invasive accounting to 54.7% (40 cases), urothelial dysplasia was seen in 6 cases (8.2%). The tumors in T_1 stage were 2.7%, Stage T_{2a} was noted in 6 cases (8.2%). Maximum invasive lesions were noted in stage T_{2b} accounting for 16.4% (12 cases). Also according to WHO/ISUP 2004, we attempted to classify the lesions according to the pattern of presentations and their variants. Six cases (8.2%) showed micro papillary differentiation and two cases presented urothelial carcinoma with nested variants. Two cases were recorded having glandular differentiation (2.7%)and six cases had squamous differentiation with two amongst them exhibiting stage IV invasion. Total of 38 cases (52%) had shown deep muscle invasion. None of the low grade urothelial lesions had exhibited any invasion.

Table 1: Chief Clinical Presentation

Hematuria	62
Abdominal Pain	11
Urgency/Frequency	39

Table 2: Age and Sex wise distribution of cases

Age (Years)	Male	Female	Total	Percentage %
01--20	3	2	5	6.80%
21-40	3	6	9	12.30%
41-60	14	9	23	31.50%
61-80	27	9	36	49.31%

Table 3: Distribution of Benign and Malignant Lesions

Lesions	No of Cases	Percentage
Benign lesions	20	27.30%
Neoplastic lesions	52	74.28%

Table 4: Distribution of Lesions

Type	No of cases	Percentage %
Acute on chronic cystitis	2	2.7
Chronic cystitis	4	5.4
Cystitis cystica	4	5.4
Cystitis glandularis	1	1.4
Eosinophilic cystitis	5	6.9
Follicular cystitis	1	1.4
Hemorrhagic cystitis	1	1.4
PUNLMP	4	5.4
Low grade papillary urothelial carcinoma	2	2.7
Polypoid Cystitis	2	2.7
Urothelial Carcinoma	38	52.0
Urothelial dysplasia	6	8.2

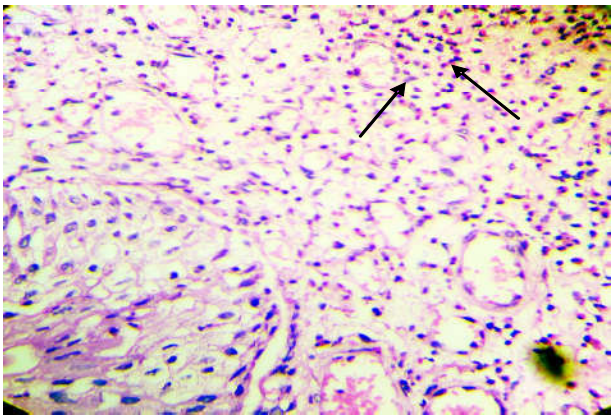

Fig. 1: Eosinophilic Cystitis with scattered eosinophils in the inflammatory infiltrate as shown by arrows. (H&E 40x)

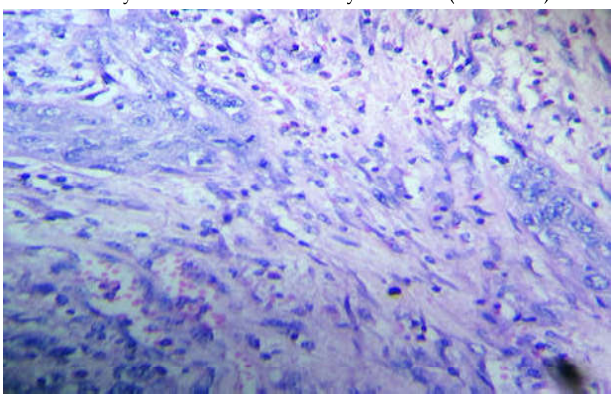

Fig. 2: Sarcomatoid Variant of Urothelial Carcinoma (H&E 40x)

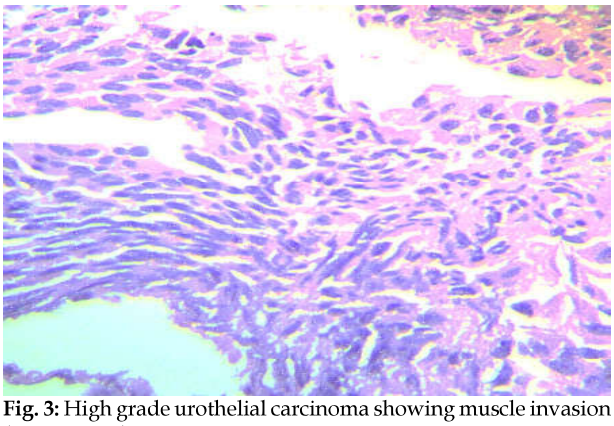

Fig. 3: High grade urothelial carcinoma showing muscle invasion (H & E 40 x)

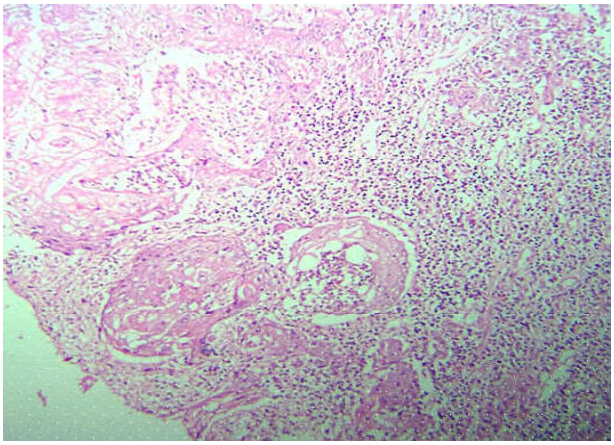

Fig. 4: Moderately Differentiated Squamous Cell Carcinoma (H&E 40x)

Discussion

The lesions of urinary bladder are responsible for significant morbidity and mortality all throughout the world. Amongst them urothelial carcinoma is the most common and accounts for 90% of all primary tumors of the bladder. With advent of technology and newer methods, cystoscopy has become the diagnostic means for patients with suspected lesions of bladder. It allows direct visualization of the lesions in the bladder mucosa and also aids in taking biopsy samples simultaneously. In 1805, Bozonni first introduced the cystoscope with a metal tube and a spark plug on the extra vesicle end. The spark plug illuminated the vesicle field. In 1929, Young and Mannon independently described the first bladder biopsy forceps by which it was possible to extract tumor tissue.[6]The cystoscopic biopsies and the approach of the pathologists helps in diagnosing and determining the treatment of the patient.

The demographic findings of the patients in the study were similar to those of other studies, especially considering the peak age of presentation of the lesion which were mostly found in the age group of 61 -80

yrs. Similar findings were seen in the study conducted by Laishram et. al [2], Thapa et al [3] and Rabia et.a l [7]. The male to female ratio reported in our study was 2:1 which was comparable to the study conducted by Laishram et al [2] (1.5:1). This was relatively less as compared to the studies conducted by Rabia et al [7] (12.9:1), Thapa et al [3] (3.8:1) and Vaidya et al [8] (4.5:1). A total of 73 cases of urinary bladder lesions were included in the study. Hematuria was the commonest clinical presentation (85%), an increased frequency and urgency was noted in (53%) of cases and few of them (15%) presented with complains of abdominal pain. Similar findings were noted by Ray et al [9] who had concluded that painless hematuria was the most common clinical presentation in patients presenting with lesions of urinary bladder.

Number of benign lesions were documented in our study. Amongst them most common were eosinophilic cystitis (6.9%), cystitis cystica and chronic cystitis (5.4%), acute on chronic cystitis (2.7%) and follicular and hemorrhagic cystitis at 1.4%. Eosinophilic cystitis as the name suggests is an inflammatory condition of the bladder, which can be of idiopathic etiology or triggered by food allergen, asthma or allergic gastroenteritis. On microscopy usually edematous lamina is noted with mixed inflammatory infiltrate predominantly comprising of eosinophils (Fig 1). Often a high absolute eosinophil count is associated [4]. Nonspecific cystitis have varied histopathological presentations – chronic cystitis, follicular cystitis and hemorrhagic cystitis. Usually they go undetected due to unawareness about the symptoms and the biopsy procedure in only performed in suspected cases of carcinoma.

Urothelial tumors account for 90% of all cancers and show marked variation from small benign lesions to aggressive carcinomas associated with high mortality. Molecular studies have suggested number of alterations and deletions in urothelial carcinomas. The most common being monosomy and deletion of 9p or 9q, mostly noted in non-invasive tumors. Deletions in 17p, which includes p53 are mostly noted in invasive urothelial carcinoma. P53 alterations are noted in majority of invasive urothelial carcinoma [4].

Amongst all lesions of urinary bladder, which were taken in the study the malignant were 74.3% (52 cases) and urinary carcinoma accounted for (80 %), which is in accordance with the studies conducted by Thapa et. al [3]. Low grade papillary urothelial carcinoma and sarcomatoid were both 4% each and six cases (12%) of urothelial dysplasia were noted in the study. These findings are similar to the studies conducted by Mahesh et.al., Mohammad M. et.al and Dravid et. al [10-12].

Urothelial carcinoma was earlier termed as Transitional cell carcinoma and has been associated with morbidity and mortality throughout the world (Fig. 3). There are two common precursor lesions i.e. noninvasive papillary tumors and flat noninvasive urothelial carcinomas [13]. Depending upon the morphology they are of two types papillary and non-papillary (flat-sessile). The noninvasive papillary carcinomas are comprising 25% of primary urothelial carcinomas of the bladder. The other variants which have been reported in our study are with glandular differentiation, micro-papillary differentiation, squamous and nested variant. Also two cases, with sarcomatoid differentiation were recorded in the study. Low grade papillary carcinoma was noted in two cases and six cases presented with urothelial dysplasia.The extent of invasionand the variants in urothelial carcinoma, defines the management and prognosis, which is different for invasive and noninvasive lesions.

In, our study six cases had presented with squamous differentiation, which is characterized by presence of nests of malignant squamous epithelium with polygonal cells, dyskeratosis, keratin pearl formation with focal inter cellular bridges (Fig. 4). Defining squamous changes is critical, since the tendency for normal and neoplastic urothelium to undergo squamous differentiation is well documented. Squamous cell carcinoma of the bladder usually arises in the setting of chronic irritation in form of smoking, schistosomiasis or causes like repetitive trauma. Squamous differentiation within urothelial carcinoma is noted in 21% of urothelial carcinoma and in 44% of tumors of renal pelvis [14]. The frequency increases with tumor grade, stage and usually associated with worse prognosis. Invariably they are resistant to chemo and radio therapy [15].

Amin and colleagues described the first report on micro papillary variant of urothelial carcinoma in the year 1994 [16]. Micro papillary variant has been introduced in the WHO classification (2004) and is characterized by slender, delicate filiform papillary processes that do not have fibro vascular cores and on cross section have glomeruloid appearance. The overall appearance is that of an inverted papillary pattern. The invasive part of the same is composed of tight clusters that are contained within the empty lacunar spaces, actually these spaces are artefactual and lack the lining epithelium. IHC staining with CD 31 and factor VIII shows that these spaces are not lined by the endothelium [16]. A significant male preponderance is noted and patients usually present with painful hematuria with advanced stage of the disease. On histopathology invasion of the muscularis

propria is invariably noted and so deeper biopsies are recommended in case the superficial biopsy show invasion of lamina propria [8,15]. In the current study, we had six cases having micro papillary differentiation and deep muscle invasion was noted in four of them. The possible differential could be metastatic micro papillary adenocarcinoma of lungs, breast and ovarian carcinoma, which need to be correlated with clinical history and specific immunohistochemistry markers. The micro papillary pattern is associated with poor prognosis and radical cystectomy is advised in view of failure with chemo and radiotherapy [15].

Two cases of Urothelial carcinoma with nested variant were identified in our study. They were confused with Von Brunn's nests, Cystitis Cystica and Nephrogenic Adenoma [15]. They were first described by Stern in 1979 as an unusual benign looking bladder carcinoma of Brunn's nest origin [17]. Usually the lesions are noted in elderly men, with clinical manifestations of hematuria, urgency and sign of urethral obstruction. On microscopy, the tumor cells are arranged in nests and abortive tubules infiltrating the lamina propria and deep muscularis propria. The tumor cells are deceptively benign looking but atypical cells are scattered and with the depth of invasion degree of nuclear atypia increases. The differential diagnosis includes prostatic carcinoma and vesical adenocarcinoma.

In the current study two cases of glandular differentiation have been reported. The entity was first described in the year 1968 [18]. Glandular differentiation is noted in all stages and grades of urothelial carcinoma. The prognosis of glandular differentiation is poor and the management of the cases is different as compared to those from metastatic adenocarcinoma. Glandular differentiation is defined by the presence of true glandular spaces within the urothelial carcinoma. They are usually of enteric or tubular types and are associated with variable mucinous production [15].

Sarcomatoid variants are a group of biphasic malignant neoplasms exhibiting morphologic evidence of epithelial and mesenchymal differentiation (Fig. 2). We had two suspected cases of urothelial carcinoma with sarcomatoid variation. Grossly they present as exophytic, polypoid lesions, filling the bladder lumen, with a dull grey solid fleshy appearance on cut section. The other sites where these tumors have been reported are renal pelvis and ureters. The morphology of sarcomatoid component in sarcomatoid carcinoma may resemble a range of mesenchymal tumors, most commonly being malignant fibrous histiocytoma and undifferentiated sarcoma, with the stroma having myxoid, hemorrhagic, vascular or desmoplastic reaction. The carcinomatous component may comprise urothelial, squamous, glandular, small cell type or unclassified carcinoma. The mesenchymal and epithelial elements are intimately mixed and gradual transition with the progression of disease may be noted from one to another [15].

A special mention needs to be made here about PUNLMP (Papillary urothelial neoplasm of low malignant potential). We have reported a total of four cases of the same. On histopathology, they present with thick urothelium, diffuse nuclear enlargement and no cytological atypia, they share a few features with papilloma. The papillae are lined by thickened urothelium, often parallel in pattern with monotonous appearing cells [13].

In our study we reported two cases of low grade papillary urothelial carcinoma, characterized by orderly appearance [13]. It is a papillary neoplasm having cytological atypia with over all orderly appearance of the papillary fronds lined by urothelium. The cells are closely places and are cohesive, however mild nuclear atypia with infrequent mitotic figures are seen. Although rare, low grade cancers can recur with evidence of invasion [19].

Urothelial dysplasia has been taken in the WHO/ ISUP 2004 classification for urothelial carcinoma in situ/ high grade dysplasia. They present with mild nuclear enlargement, slight disorganization of architecture and occasional mitotic figures [13,19]. Benign urothelium with reactive changes and urothelial carcinoma in situ are the most common differentials.

Tumor staging and grading are the two main factors for recurrence, progression and defining the treatment options [21]. In our study, we defined as per the TNM staging, majority of tumors were invasive accounting to 54.7% (40 cases), urothelial dysplasia was seen in 6 cases (8.2%). The tumors in T_1 stage were 2.7%, Stage T_{2a} was noted in 6 cases (8.2%). Maximum invasive lesions were noted in stage T_{2b} accounting for 16.4% (12 cases). In the study conducted by Vaidya et al 24 cases had presented with muscle invasion out of 67 cases [8]. Similar findings were observed by Laishram et al [2]. Remarkable progress has been made in the standardization of bladder neoplasm classification and reporting. Accurate staging using the American Joint Committee on Cancer/International Union Against Cancer (AJCC/ UICC) TNM system is essential for patient management, and has been reinforced by clinical evidence in recent years. It is now recognized that 'superficial' bladder carcinomas are a heterogeneous group of tumors with diverse

biological and clinical manifestations. The term 'superficial,' therefore, is no longer used for bladder tumor nomenclature. Recognition of diagnostic pitfalls associated with lamina propria invasion is critical for the evaluation of bladder tumor specimens. An estimated 40% of tumors, especially deeply invasive tumors metastasize to regional lymph nodes. Hematogenous dissemination, principally to the liver, lungs and bone marrow has been recorded in the literature [13].

Conclusion

The study revealed wide spectrum of non-neoplastic and neoplastic lesions. Eosinophilic cystitis, was the commonest non neoplastic lesion and urothelial carcinoma neoplastic. It presents with various variants and morphologies which may cause diagnostic difficulty and the histological differentiation can be variable. It is critical, to identify and properly quantify the tumor differentiation areas as the prognosis of the patient can accordingly vary. The majority of the cases of urothelial carcinoma in our study presented with lamina propria and muscle invasion and it is worth mentioning that pathological grade and muscle invasion are the most valuable prognostic predictors. The importance of including muscle in cystoscopic biopsies is critical. A general awareness about lifestyle changes and hematuria is needed so that early detection of the bladder carcinoma can be done.

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