HISTOPATHOLOGICAL STUDY OF CYSTOSCOPIC BLADDER BIOPSIES IN A TERTIARY CARE CENTER

Rachana Dhakal[1], Hem Nath Joshi[2], Ramesh Makaju[3], Shailendra Sigdel[4]*

Affiliation

1. *Assistant Professor, Department of Pathology, Kathmandu University School of Medical Sciences, Nepal.*
2. *Associate Professor, Department of Surgery, Kathmandu University School of Medical Sciences, Nepal.*
3. *Associate Professor, Department of Pathology, Kathmandu University School of Medical Sciences, Nepal.*
4. *Assistant Professor, Department of CTVA, Tribhuvan University Institute of Medicine, Nepal.*

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**** Corresponding Author***

Dr. Rachana Dhakal

Assistant Professor

Department of Pathology

Kathmandu University School of Medical Science, Nepal

Email ID: sigdelrachana@gmail.com

ORCID ID: https://orcid.org/0000-0003-2189-8369

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ABSTRACT

Introduction

Non-neoplastic urinary bladder lesions are not life-threatening, but are an important source to cause clinical symptoms and signs. However, neoplasms of the bladder are a source of morbidity, mortality, and exhibit more clinical challenges. Cystoscopy provides overall information about an anatomical/pathological condition of the urinary bladder which will be helpful for patients' management. A cystoscopic biopsy is a primary diagnostic tool for diagnosing urinary bladder cancer.

Objectives

The objective of the study was to find the frequency and histomorphological characteristics of urinary bladder lesions in Dhulikhel Hospital, to find the clinical presentation of urinary bladder lesions and to grade the urothelial tumors based on the World Health Organization (WHO)/ International Society of Urological Pathology (ISUP) classification 2004.

Methodology

This was a retrospective, cross-sectional, observational study carried out in the Department of Pathology, Dhulikhel Hospital-Kathmandu University Hospital. Convenient sampling was done. All cystoscopy biopsies received from January 2014 to December 2018 were studied. All tissue blocks were retrieved, cut, and stained with Hematoxylin and Eosin. The stained slides were examined under a light microscope by the primary investigator.

Result

A total of 70 cystoscopic biopsies were analyzed. The majority of patients 20 (28.6%) were in the age group between 60 and 69 years and males were predominant 43 (61.4%). The neoplastic lesions constituted 40 (57.1%) of all bladder lesions, among them urothelial carcinoma accounted for 38 (54.2%). Similarly, chronic cystitis 27(38.6%) was the most common non-neoplastic lesion.

Conclusion

The study found that the neoplastic lesions were commonly encountered in urinary bladder lesions. Among them, low-grade urothelial carcinoma was the most common bladder tumor. However, most of the non-neoplastic lesions were inflammatory in origin. Cystoscopy combined with histomorphological examination helps in the early detection of bladder lesions.

KEYWORDS

cystoscopy, histopathology, neoplasm, urinary bladder.

INTRODUCTION

Neoplastic and non-neoplastic lesions of the urinary bladder are common clinical conditions encountered by urologists in daily practices. Cystitis, malakoplakia, urachal lesions, and tuberculosis are common non-neoplastic lesions.[1] Non-neoplastic lesions of the bladder, particularly inflammatory lesions (cystitis) present with clinical symptoms and signs. These lesions are more disabling. But, neoplasms of the bladder are clinically challenging and have high morbidity and mortality.[2]

Bladder carcinoma is the second most common malignancy of the genitourinary tract after prostate cancer in males and represents a heterogeneous group of neoplasms.[1] In the western world it is the fourth most common malignant tumor and it accounts for 5-10% of all malignancies among males in Europe and the United States.[3] In South Asia, the reported rate of bladder cancer is about 2.1 per 100,000.[4] The majority of these lesions occurred in patients over the age of 50 years. Men are more commonly affected than women (3 to 4:1).[5,6] Bladder cancers are strongly associated with exposure to smoking, environmental toxins, and aging.[7] Although, the spectrum of bladder cancer is diverse, the majority are urothelial tumors. The other tumors are squamous cell carcinoma (SCC), adenocarcinoma, and rare varieties like small cell carcinoma. The recurrence rate for these tumors ranges from 50% to 70%, and 10% to 15% of cases progress to muscle invasion over 5 years.[8,9] Although the clinical presentation of bladder lesions is varying, gross and microscopic hematuria are seen in more than 75% of bladder cancer patients.[10]

Focal bladder mass or diffuse wall thickening is the pathological changes seen in the bladder. Focal masses may be either neoplastic or might have developed secondary to congenital, inflammatory, idiopathic, or infectious sources. Besides, tumor-like lesions of the urinary bladder are diagnostically challenging. However, if such lesions are misdiagnosed, it may result in serious consequences in patient management. Since, clinical, gross, and radiologic findings usually overlap, histomorphological evaluation is important for definitive diagnosis.[11]

The histologic grade, differentiation, and depth of invasion are important for the assessment of bladder tumors. The patient's survival rates, recurrences and progression depend on tumor grading and staging system.

The first widely accepted grading system for papillary urothelial neoplasms was the World Health Organization (WHO) classification system, which divided urothelial tumors into 4 categories: papilloma, grade 1 carcinoma, grade 2 carcinoma, and grade 3 carcinoma. In 1998, a revised system of classifying papillary urothelial neoplasms of the urinary bladder was proposed.[12] This system was formally adopted by the 1998 WHO/International Society of Urological Pathology [ISUP] classification. In 2004, a classification system for noninvasive papillary urothelial neoplasms was adopted which was similar to the 1998 WHO/ISUP classification system.[13] This new system separates noninvasive papillary urothelial neoplasms into 4 categories: papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade carcinoma, and high-grade carcinoma. This grading system standardizes the pathological diagnosis of noninvasive urothelial papillary neoplasms which provides the foundation of treatment for clinicians and offers proper patient management.[14]

Apart from cystoscopy and biopsy other common methods to diagnose bladder lesions are imaging, urine cytology, fluorescence in situ hybridization, and urine protein detection.[15,16]

But cystoscopy remains a standard diagnostic tool for direct visualization of the bladder mucosa and biopsies of the suspected lesions. Cystoscopy biopsies ensure a material necessary for histopathological diagnosis. With a histomorphological diagnosis, the degree of differentiation, depth of tumor invasion, and the prognosis of the disease can be assessed.[17]

The objective of study was to find the frequency and histomorphological characteristics of urinary bladder lesions in Dhulikhel Hospital, to find the clinical presentation of urinary bladder lesions and to grade the urothelial tumors based on the WHO / ISUP classification 2004.

METHODOLOGY

This cross-sectional, observational retrospective study was carried out after obtaining approval from the Institutional Review Committee at Dhulikhel Hospital - Kathmandu University Hospital (DH-KUH) (approval number: 48/19). The sample size was calculated using the following formula:

$$n = Z^2 \times p \times (1-p)/e^2$$
$$= (1.96)^2 \times 0.04 \times 0.96/(0.05)^2$$
$$= 59$$

Where,

Z = 1.96 for 95% Confidence Interval

p = population proportion, 4%

e = margin of error

In this study, all the cystoscopy biopsies received in the Department of Pathology at DH-KUH from January 2014 to December 2018 were retrospectively studied. The sample proportion was calculated with the cystoscopy biopsy samples that came in the Department of Pathology, DH-KUH over the past few years, which was 3.5 %. Thus, the population proportion for the study was taken as 4%. For this study, we enrolled 70 patients.

The patient's demographic data, clinical history, and provisional clinical diagnosis were extracted from the patient's record file and histopathological forms. The autolyzed and inadequate samples were excluded from the study.

For this study, the paraffin tissue blocks were retrieved. They were cut into five-micron sections and stained with Hematoxylin and Eosin. The histopathological features of cystoscopy biopsies were studied and urothelial tumors were graded using the WHO/ISUP classification (2004).

Data was collected in *Pro-forma* and entered into Microsoft Excel spreadsheet. Data analysis was done with Microsoft

Excel version 2019. Nominal data were presented as number (N) and percentage (%) and continuous were presented as mean with standard deviation.

RESULTS

The age of the patients enrolled in the study ranged from 9 to 92 years. The mean age of patients was 59.7±15.25years, while that of the male was 63.19 ± 9.00 and females was 54.37 ± 16.44 years. The majority of patients 20 (28.6%) were in the age group between 60 and 69 years and males were predominant 43 (61.4%). [Fig. 1] The commonest clinical presentation was hematuria. [Fig. 2]

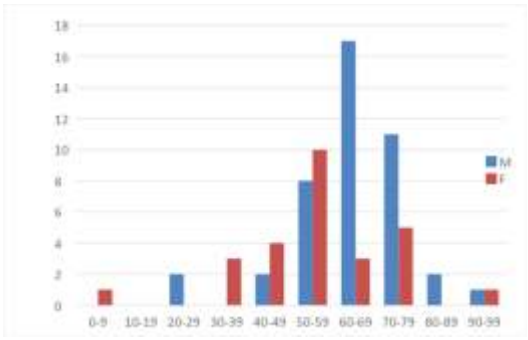

Figure 1: Age and gender-wise distribution.

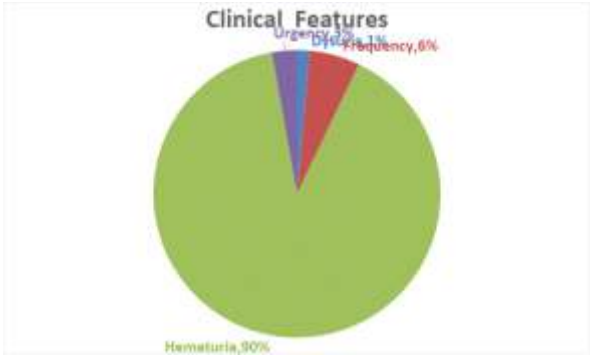

Figure 2: Distribution of cases with respect to clinical features

Out of 70 cases, 40 (57.1%) were neoplastic lesions and 30 (42.9%) were non-neoplastic lesions. Among neoplastic lesions, urothelial carcinoma constituted 38 (54.2%) followed by SCC 2 (2.9%). Out of 30 non-neoplastic lesions, chronic cystitis 27(38.6%) was the commonest lesion. [Table 1]

Table 1: Histopathological diagnosis of cystoscopy bladder biopsies

Histopathological diagnosis	Number of cases N(%)
Non-neoplastic lesions	
Acute cystitis	2(2.9%)
Chronic cystitis	27(38.6%)
Granulomatous cystitis	1(1.4%)
Neoplastic lesions	
Urothelial neoplasm	
High-grade Papillary Urothelial carcinoma	15(21.4%)
Low-grade Papillary Urothelial carcinoma	22(31.4%)
Papillary Urothelial Neoplasm of Low Malignant Potential	1(1.4%)
Squamous cell carcinoma (SCC)	2(2.9%)
Total	**70(100%)**

According to the WHO/ISUP classification (2004), in this study low-grade urothelial carcinoma was the commonest urothelial tumor 22 (57.9%) followed by high-grade urothelial carcinoma 15 (39.5%) and PUNLMP 1(2.6%). [Table 2]

Among urothelial neoplasm, lamina propria invasion was 31(83.8%) and muscular invasion was 12 (32.4%). [Table 3]

Table 2: Histological grading of Urothelial Neoplasm as per the WHO/ISUP 2004

Grade	Number of cases N(%)
Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)	1(2.6%)
Low-grade Papillary Urothelial Carcinoma	22(57.9%)
High-grade Papillary Urothelial Carcinoma	15(39.5%)
Total	**38(100%)**

Table 3: Distribution of cases as per the invasion in the urothelial carcinoma.

Invasion	Present	Absent
Lamina propria	31(83.8%)	6 (16.2%)
Muscular invasion	12 (32.4%)	25 (67.6%)

DISCUSSION

The combination of cystoscopy, histopathology, and urine cytology is a diagnostic and monitoring tool for bladder lesions.[15,16] Cystoscopy helps in localizing the bladder tumors as well as detecting low-grade papillary lesions. However, cystoscopy alone cannot detect carcinoma in situ. Likewise, tumor grade and depth of invasion cannot be assessed. Hence, histopathology is the gold standard method for diagnosing bladder lesions.[18] Besides, histopathology also provides information to the clinician regarding the impact of the treatment, which may help to change the treatment modality.

Our study found that male has higher propensity to the bladder lesion (male to female ratio1.6:1). Similar to our findings, a study done in Pakistan by Hasan et al. (2.58:1) and in Nepal by Thapa et al. (2.78: 1) found that the males were more commonly affected by the bladder lesions.[19,20] Male dominance in the bladder lesion is probably due to higher exposure to smoking, occupational hazards, and environmental toxins.[7]

The risk of developing bladder cancer at 75 years of age is 2% to 4% for men and 0.5% to 1% for women.[21] Our study showed that the lesions are commonly seen in the age group of 60 to 69 years. The study done by Vaidya et al. has a similar finding, where 33.73% of the cases were distributed between the age group of 61-70 years.[22] The mean age of

patients in our study was 59.7±15.25years which was similar to the findings of existing literature.[10,21,23]

The earliest and most common symptom of primary bladder cancer is hematuria. The nature of hematuria includes full-course, intermittent, and painless gross hematuria, sometimes accompanied by blood clots.[15,24]Irritative urinary tract signs and symptoms, such as urinary frequency, urgency, hesitancy, and dysuria are less commonly encountered in bladder cancer. These irritative urinary signs and symptoms mimic urinary tract infections. Hence, patients may be initially diagnosed with a urinary tract infection and delay a bladder cancer diagnosis. In our study, 90%of the patient presented with hematuria which was similar to the results of various other studies where more than 75% of bladder tumor patients presented with hematuria.[10,25,26]

A low-grade papillary urothelial carcinoma consists of slender papillae with frequent branching and variation in nuclear polarity. The nuclei show enlargement and irregularity with vesicular chromatin, and nucleoli are often present. Mitotic figures may occur at any level. Such findings are considered as grade 1 or 2 carcinomas in the WHO 1973 classification, however in 2004 WHO/ISUP they are assigned as low-grade papillary urothelial carcinoma.[13,27] In high-grade papillary urothelial carcinoma, fused papillae with loss of polarity, moderate to marked pleomorphism, multiple prominent nucleoli, and frequent mitosis are present. Such tumors are classified as grade 3 in the WHO 1973 classification. However, in the WHO/ISUP 2004 classification, they are considered as high grade papillary urothelial carcinoma.[27]

Among the bladder lesions, in our study urothelial carcinoma constituted (54.2%) which is similar to the findings of the study carried out by Dravid et al.(53.4%) and Thapa et al. (58.6%).[18,20] Similarly, low-grade papillary urothelial carcinoma constituted (57.9%) which is similar to the study of Laishram et al (53.8%)and Thapa et al (50%).[20,28] In the present study, high grade papillary urothelial carcinoma was (39.5%) is comparable to the study of Vaidya et al (32.7%), Laishram et al (34.61%), and Thapa et al (30.3%).[20,22,28]

In our study and other studies done in SouthEast Asia[18,20,29] the frequency of SCC is low. However, the prevalence of SCC is relatively high in the African region. This may be due to the high prevalence of Schistosomiasis in that region which is associated with SCC.[13,30] The bladder urothelium changes during Schistosoma hematobium infection. It leads to hyperplasia, ulceration, dysplasia, squamous metaplasia, and frank SCC. The tumor suppressor gene p53 has a significant role in many cancers, including bladder cancer and particularly in schistosomal bladder cancer.[31]

In our study, the frequency of PUNLMP is lower (2.6%) than the findings of Dravid et al. (5.4%), Laishram et al. (7.69%), and Vaidya et al. (10.28%).[18,22,28] The WHO 2004 classification system defines PUNLMP as a papillary urothelial tumor that resembles the exophytic urothelial papilloma with increased cellular proliferation exceeding the thickness of normal urothelium.[32] These lesions carry biologically a low risk of progression. Many of these patients often presented with high-grade tumor recurrence.[33,34] Hence, early recognition of these tumors is important to prevent progression and recurrence.

Bladder carcinoma with muscular invasion is an aggressive epithelial tumor that has a high rate of early systemic dissemination and poor long-term survival. Almost 50% of these patients develop metastases.[35,36] One-third of newly diagnosed bladder cancers are advanced at presentation. Within 5 years, another 15% to 30% of high-grade superficial tumors progress to muscle-invasive tumors .[35-37]

In our study muscular invasion was seen in 32.4% cases of urothelial carcinoma which was comparable with the finding of Thapa et al.[20] (24.5%). Lamina propria invasion in our study was seen in (83.8%) cases of urothelial carcinoma which is consistent with the finding of a study performed by Sathya et al.[38] (87%). Lack of smooth muscle in the cystoscopy biopsy specimen may lead to understating of tumors.[30] Hence, the inclusion of smooth muscle in each biopsy should be prioritized.

Early detection and intervention of the urinary bladder lesions can help to constrain the disease progression or to cure the disease completely. Imaging techniques alone or other diagnostic modalities may not detect bladder cancer at an early stage. Cystoscopy with the histopathological examination helps early detection as well as to identify the variant of bladder cancer. With the histopathological findings, clinicians can decide the modalities of treatment such as intravesical treatments, chemotherapy or can decide the time of radical cystectomy and urinary diversion. The early identification of the aggressive tumor is extremely important from the treatment point of view. For example, high-grade recurrent carcinoma in situ, micropapillary disease, or extensive high-grade T1 disease, early cystectomy would be rational.

CONCLUSION

Most of these bladder lesions were common in male and present as hematuria. Neoplastic lesions were common bladder lesion. Among neoplastic lesions, low-grade urothelial carcinoma was the most common bladder tumor. Among non neoplastic lesions, chronic cystitis were common. Cystoscopy and histopathological examination of bladder biopsies are important in the diagnosis of various bladder lesions.

LIMITATIONS OF THE STUDY

This was a single center-based study. Thus, other studies with larger sample sizes are recommended from different hospitals to confirm our findings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

FINANCIAL DISCLOSURE

The authors declare no financial disclosure.

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