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Histopathological Spectrum Of Lesions In The Urinary Bladder: A Retrospective Study

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ABSTRACT

Introduction: The urinary bladder is susceptible to a broad spectrum of non-neoplastic and neoplastic conditions, which often overlap both clinically and radiologically. Histopathologically, these lesions display varied morphological features, with certain benign conditions closely mimicking neoplasms, necessitating the importance of meticulous histopathological evaluation. While non-neoplastic conditions impact the quality of life, malignant neoplasms present life-threatening implications. Comprehensive histopathological evaluation, integrated with clinical and radiological findings and careful distinction of potential mimickers, forms the cornerstone of accurate diagnosis and optimal patient management.

Objective: To study and classify the histopathological spectrum of urinary bladder lesions into non-neoplastic and neoplastic categories, and to further classify neoplasms according to the WHO 2022 Histological Classification.

Methodology: This retrospective study was conducted from January 2018 to July 2024. Specimens included bladder biopsies, transurethral resection of bladder tumors (TURBT), and cystectomies.

Results: This retrospective study examined 42 urinary bladder specimens, with 34 identified as neoplastic (81%) and 8 as non-neoplastic (19%). The male-to-female ratio was 2.5:1, and the most affected age group was 51–60 years, predominantly male. Hematuria was the most common symptom, followed by dysuria, increased urination frequency, and flank pain. Follicular cystitis was the leading non-neoplastic lesion (42.8%), followed by chronic cystitis (25%), with one case each of granulomatous cystitis, cystitis cystica et glandularis, and malakoplakia. Neoplastic lesions were predominantly non-invasive urothelial neoplasms (67.6%), particularly Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP) (35.3%), followed by invasive urothelial neoplasms (26.4%), including 8 high-grade and 1 low-grade case, with muscularis propria invasion in 4 cases. Additionally, single cases of Squamous cell carcinoma and Embryonal rhabdomyosarcoma were observed.

Conclusion: A diverse array of lesions manifests within the bladder, with urothelial tumors notably prevailing, followed by cystitis. The gold standard for diagnosis is histopathological analysis of bladder specimens, which helps identify non-neoplastic and neoplastic conditions, grade and stage tumors, and classify neoplasms for treatment purposes.

Keywords: *Bladder, urothelium, neoplastic, non-neoplastic, cystitis*

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1. INTRODUCTION

A vast range of lesions affect the urinary bladder, including infections, inflammatory diseases, metaplastic lesions, benign and malignant tumors, and metastatic lesions [1]. Tumors arising from the bladder can be benign or malignant, with the latter being more prevalent [2]. Neoplastic lesions result in higher morbidity and mortality rates than non-neoplastic lesions, which are incapacitating [2].

Urinary bladder cancer ranks as the 10th most common cancer globally and is the 13th most common cause of cancer-related mortality [3]. In 2020, there were an estimated 573,000 new cases of bladder cancer and 212,000 bladder cancer deaths globally, representing approximately 2% of all cancer deaths and 3% of newly diagnosed cancers [3, 4]. Early detection leads to effective treatment and a significant 5-year survival rate. In India, approximately 5,403 women and 20,470 men are diagnosed annually, with a cumulative risk of one in 250 for men and one in 1,014 for women [1, 5, 6].

Bladder lesions often present with overlapping clinical features and radiological findings, making accurate diagnosis challenging [7]. Cystoscopy is the primary diagnostic tool for evaluating patients suspected of having bladder tumors. It enables direct visualization of the bladder mucosa and facilitates biopsy of suspicious areas [8]. However, conventional cystoscopy has limitations; it may miss flat lesions, such as carcinoma in situ (CIS), and cannot reliably differentiate benign from malignant tumors before biopsy [9, 10].

Bladder cancer exhibits marked histological diversity [9, 11]. Therefore, a thorough histopathological evaluation is essential for categorization, which may have clinical and therapeutic implications.

To achieve an accurate diagnosis of urinary bladder lesions, data from multiple disciplines, including urology, radiology, and surgical pathology, must be integrated. Clinical features, cystoscopic evaluation, and detailed histopathological analysis form the backbone of contemporary bladder cancer diagnosis and management [12].

2. OBJECTIVES

- To study and analyze the histopathological spectrum of urinary bladder lesions and categorize them into non-neoplastic and neoplastic lesions.
- To classify urinary bladder neoplasms according to the WHO 2022 Histological Classification.

3. MATERIALS AND METHODS

A retrospective study was conducted on 42 cases, which included bladder biopsies, TURBT, and cystectomy specimens, received at the Department of Pathology at Rajarajeswari Medical College and Hospital in Bengaluru, Karnataka, India. Retrospective data were collected over a period of six years (January 2018 to July 2024). This study is approved by the Institutional Ethical Committee (reference number RRMCH-IEC/347/2024)

Inclusion Criteria

All cystoscopic bladder biopsies, TURBT specimens, and radical cystectomy specimens received at the histopathology division of the department during the study period were considered for the study

Exclusion Criteria

Biopsies that were inadequate or inconclusive were excluded from the study.

4. METHOD OF DATA COLLECTION

Requisition forms were used to retrieve the clinical data. Each specimen was routinely fixed in 10% buffered formalin for 24 hours and processed according to standard procedures. Multiple sections with a thickness of 3-5 microns were obtained and stained using hematoxylin and eosin. A comprehensive histopathological analysis was conducted. Based on microscopic examination, the lesions were classified as neoplastic or non-neoplastic. The 2022 WHO classification of bladder tumors was utilized to categorize the malignant lesions.

5. DATA ANALYSIS

The data collected were analyzed using descriptive and inferential statistics with the statistical software SPSS v23 and MS Excel. Descriptive statistics, such as frequencies and percentages, were utilized to summarize the data.

6. RESULTS

A total of 42 urinary bladder specimens were studied, including 6 cystoscopic biopsies, 35 TURBT specimens, and 1 radical cystectomy specimen. Of these, 34 cases (81%) were classified as neoplastic and 8 cases (19%) as non-neoplastic [Graph 1]. Bladder lesions commonly presented in the sixth decade of life, irrespective of the histology. Among the neoplastic lesions, the 51–60 year age group accounted for the highest number of cases (10 cases, 29%), followed by the 61–70 year age group (9 cases, 26%). In contrast, non-neoplastic lesions were more evenly distributed across all age groups [Graph 2]. The overall male-to-female ratio was 2.5:1, with a male predominance observed in both the neoplastic (70%) and non-neoplastic (75%) categories [Graph 3].

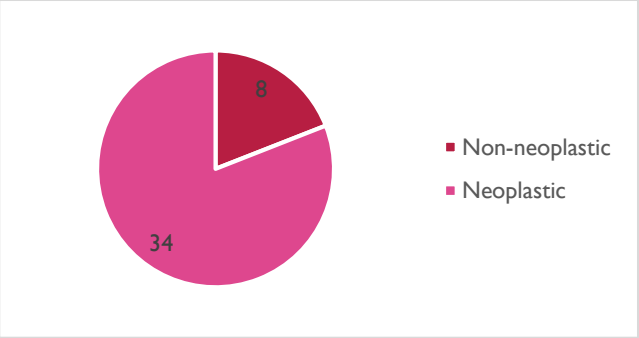
Hematuria was the most frequent clinical presentation among patients with neoplastic lesions, observed in 91% of cases. In contrast, dysuria was more commonly reported in patients with non-neoplastic lesions, accounting for 75% of the cases.

Additional symptoms noted in both groups included increased urinary frequency and flank pain [Graph 4].

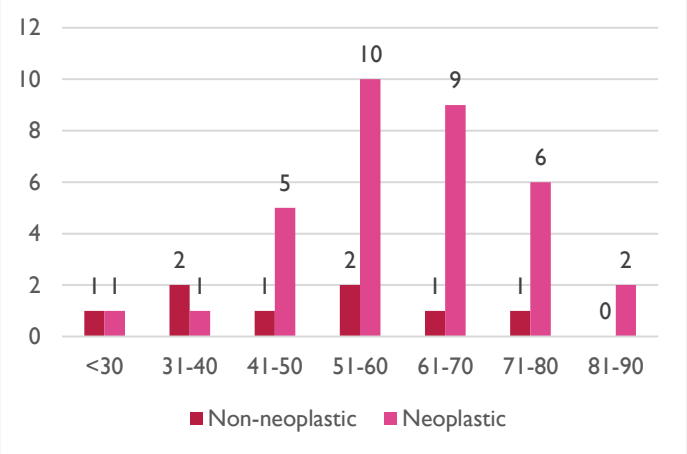
Radiological evaluation (Ultrasonography (USG), Contrast-enhanced computed Tomography (CECT), and cystoscopy) demonstrated growth in neoplastic lesions, whereas polypoidal growth was observed in two non-neoplastic cases: malakoplakia and cystitis cystica et glandularis. In 31 cases (73.8%), the lesions were located on the lateral bladder wall, followed by posterior wall involvement in 11 cases (26.2%).

Among the non-neoplastic lesions, follicular cystitis was the most commonly encountered, 3 cases, followed by chronic non-specific cystitis, 2 cases. 1 case each of malakoplakia, cystitis cystica et glandularis, and granulomatous cystitis were also identified, reflecting the histological diversity of non-neoplastic bladder pathology [Table 1].

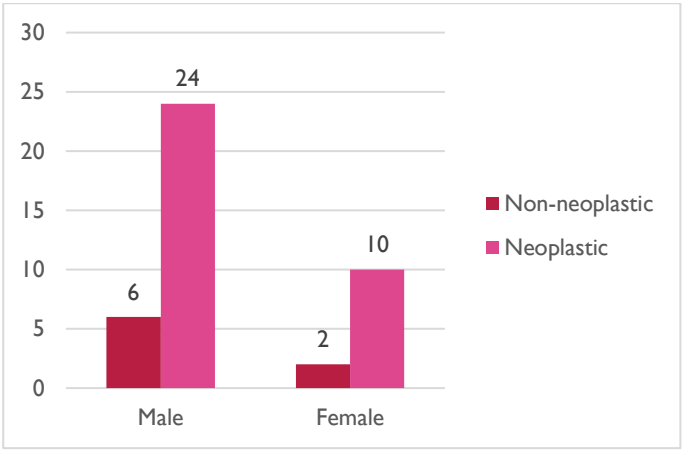
Urothelial tumors predominated among neoplastic lesions, accounting for 32 of 34 cases (94.1%). Non-invasive urothelial neoplasms comprised 23 cases (67.7%), with PUNLMP being the most frequent subtype (12 cases, 35.3%), followed by low-grade non-invasive papillary urothelial carcinoma (8 cases, 23.6%). Invasive urothelial neoplasms accounted for 9 cases (26.5%), including 6 conventional invasive urothelial carcinomas (17.7%), 2 with squamous differentiation (5.9%), and 1 poorly differentiated variant (2.9%). Single cases (2.9% each) of squamous cell carcinoma and embryonal rhabdomyosarcoma were also observed [Table 2].



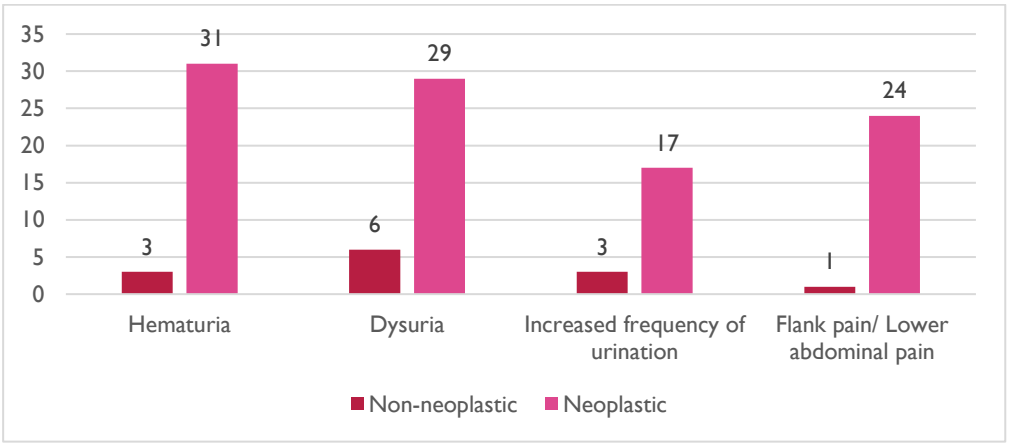
Graph 1: Distribution of cases



Graph 2: Age-wise distribution



Graph 3: Gender-wise distribution



Graph 4: Clinical presentation

Table 1: Distribution of non-neoplastic lesions

Non-neoplastic lesions	No. of cases	Percentage (%)
Chronic non-specific cystitis	2	25
Follicular cystitis	3	37.5
Cystitis cystica et glandularis	1	12.5
Malakoplakia	1	12.5
Granulomatous cystitis	1	12.5
Total	8	100

Table 2: Distribution of neoplastic lesions

Neoplastic lesions	No. of cases	Percentage (%)
1. UROTHELIAL TUMORS (A) **Non-invasive urothelial neoplasms**		
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	12	35.3
Non-invasive papillary urothelial carcinoma, low-grade	8	23.6
Non-invasive papillary urothelial carcinoma, high-grade	3	8.8
(B) Invasive urothelial neoplasms		
Invasive urothelial carcinoma	6	17.7
Urothelial carcinoma with squamous differentiation	2	5.9
Urothelial carcinoma, poorly differentiated	1	2.9
2. SQUAMOUS CELL CARCINOMA	1	2.9
3. MESENCHYMAL TUMOR		
Embryonal Rhabdomyosarcoma	1	2.9
Total	34	100

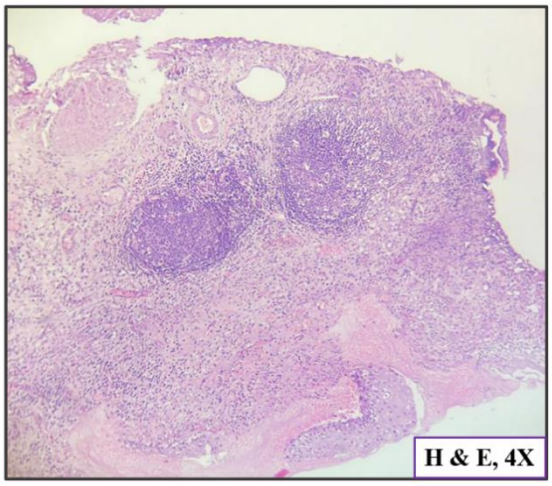


FIGURE 1: Follicular cystitis

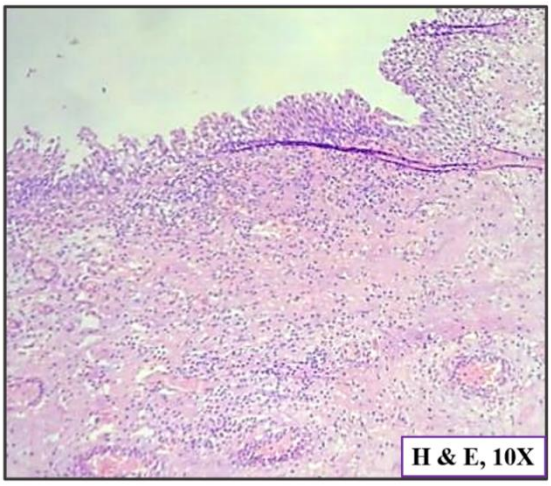


FIGURE 2: Chronic non-specific cystitis

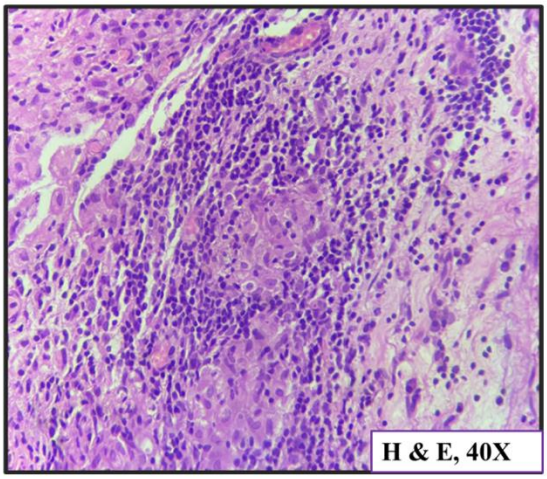


FIGURE 3: Granulomatous inflammation post BCG therapy

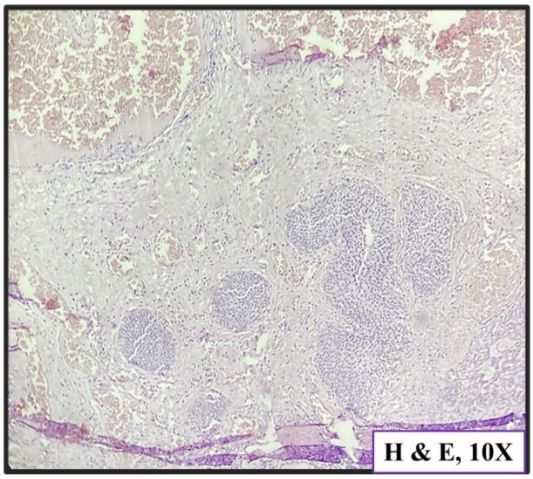


FIGURE 4: Cystitis cystica

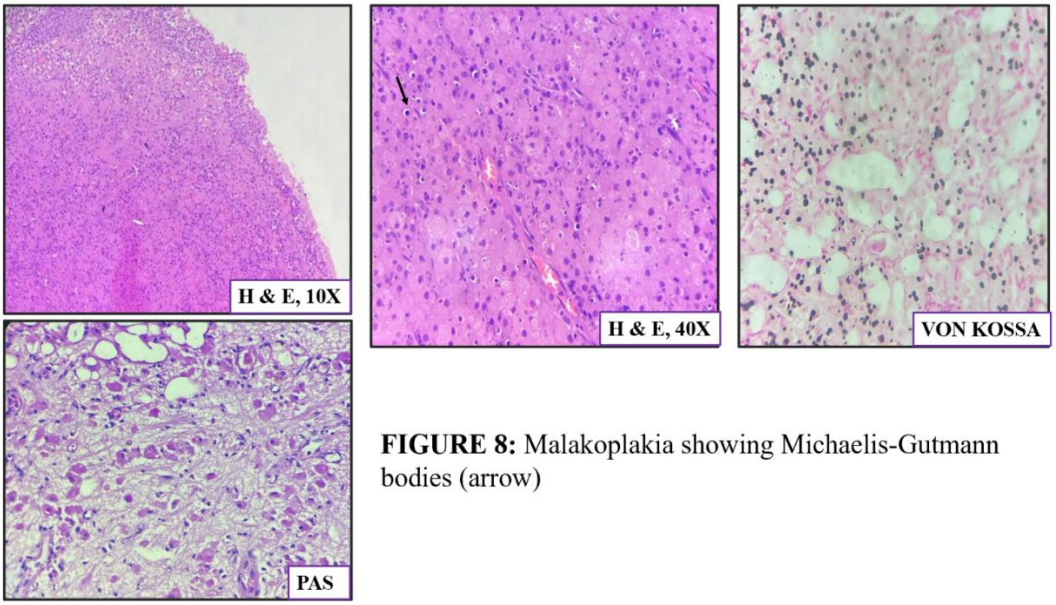


FIGURE 8: Malakoplakia showing Michaelis-Gutmann bodies (arrow)

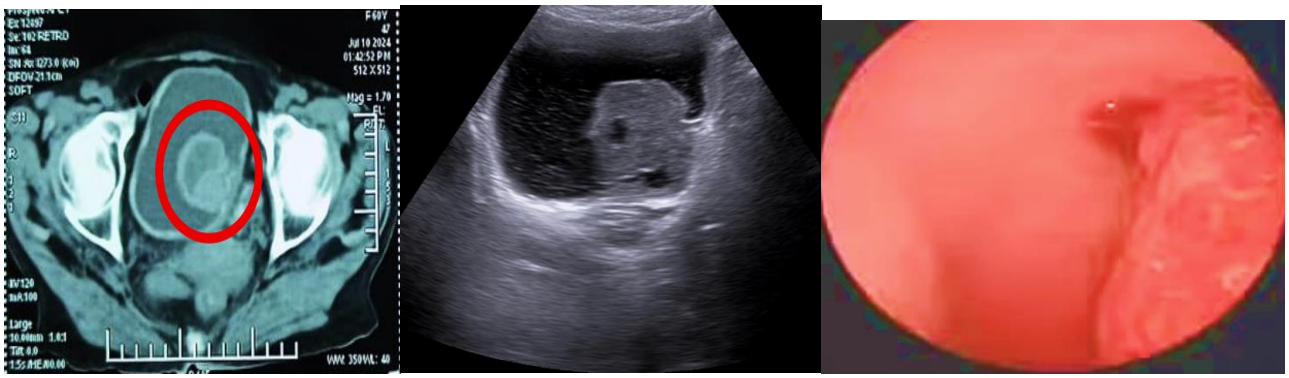


FIGURE 5: USG- Polypoidal mass in the Left lateral wall projecting into the urinary bladder

FIGURE 6: CECT KUB- Lateral bladder wall shows polypoidal pedunculated mass projecting into the bladder

FIGURE 7: Cystoscopy- A large nodular pedunculated mass visualized arising from the Left Lateral wall of the bladder.

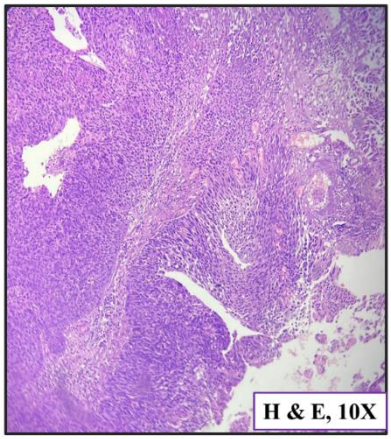


FIGURE 9: Invasive urothelial carcinoma

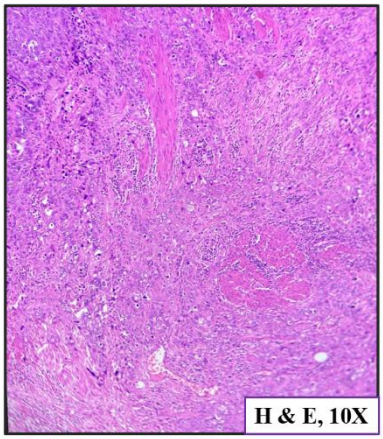


FIGURE 10: Urothelial carcinoma, poorly differentiated

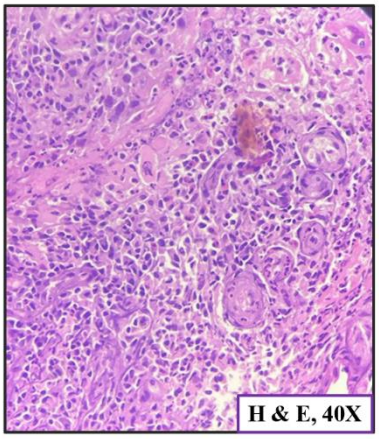
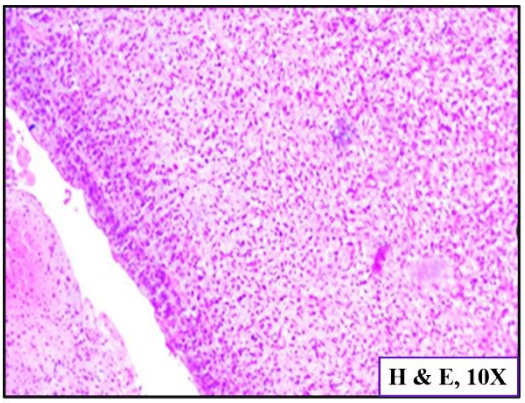
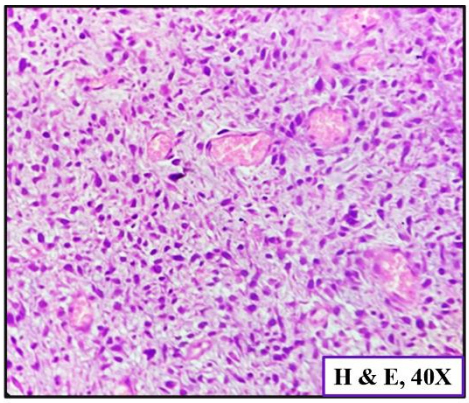


FIGURE 11: Urothelial carcinoma With squamous differentiation





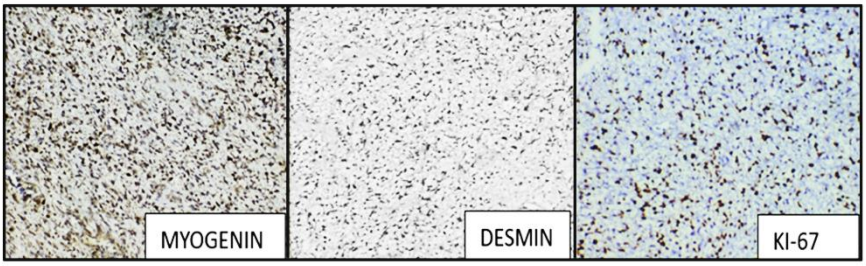


FIGURE 12: Embryonal Rhabdomyosarcoma

7. DISCUSSION

Urinary bladder lesions encompass a broad histopathological spectrum, with many benign and malignant entities exhibiting overlapping clinical and radiological features, thereby posing challenges to accurate diagnosis [7, 9]. A comprehensive clinical history is essential for interpreting bladder specimens, as factors such as kidney stones, recent urinary tract procedures, infections, or obstructions can impact biopsy results in patients with hematuria [13]. Cystoscopic assessment helps evaluate the characteristics and extent of lesions; however, despite its common use and general reliability, it has limitations, especially when it comes to detecting flat urothelial neoplasms. These constraints underscore the need for histopathological examination [7,9]. Moreover, certain benign conditions may closely resemble invasive carcinoma on histology, necessitating meticulous histomorphological assessment to ensure diagnostic precision and guide optimal clinical management [7].

In this study, a total of 42 urinary bladder specimens were analyzed, comprising 6 cystoscopic biopsies, 35 TURBT specimens, and 1 radical cystectomy specimen.

This study demonstrated a male predominance with a male-to-female ratio of 2.5:1, consistent with the findings observed by Kumar K et al., [14]. Hematuria was the most frequent clinical presentation in the neoplastic group, observed in 31

patients (91.1%), compared to only 3 patients (33.3%) in the non-neoplastic group. Dysuria was more frequently reported in non-neoplastic lesions, affecting 6 patients (66.7%), whereas it was documented in 29 patients (85.3%) with neoplastic lesions. Increased urinary frequency was noted in 17 neoplastic cases (50.0%) and 3 non-neoplastic cases (33.3%). Flank pain or lower abdominal pain was present in 24 neoplastic cases (70.6%) and only 1 case (11.1%) in the non-neoplastic group, respectively. Pokar R et al., had observed that the commonest clinical symptom was painless hematuria, followed by increased frequency of micturition [21].

Among the 42 cases examined, the majority were neoplastic, accounting for 34 cases (81%). These cases were most commonly found in the age group of 51–60 years, which included 10 cases (29.4%). This was followed by the 61–70-year age group, which comprised 9 cases (26.5%), similar to that reported by Kumar K et al., Susmitha S et al., and Pandey et al., [14,15, 16]. The youngest age with neoplastic lesion was in a 2-year-old, diagnosed with Embryonal Rhabdomyosarcoma; however, this was in contrast to other studies, in which the youngest age group was not below 20 years.

In the present study, radiological assessment (USG, CECT, and cystoscopy) demonstrated growth in neoplastic lesions, while two non-neoplastic cases—malakoplakia and cystitis cystica et glandularis—presented as polypoidal growths that mimicked neoplasms.

Lesions were most frequently located on the lateral bladder wall (31 cases, 73.8%), followed by the posterior wall (11 cases, 26.2%). These findings align with those of Pandey SK et al., who also reported a higher prevalence of lateral wall involvement than posterior wall involvement [16].

Among the wide spectrum of non-neoplastic lesions, the most common lesion observed was cystitis, consistent with the study by Singhal P et al., and Suba G et al., [7, 17]. Follicular cystitis [Figure 1] was the most common, accounting for 3 cases (37.5%), followed by chronic cystitis [Figure 2] in 2 cases (25%). Cystitis cystica et glandularis, malakoplakia, and granulomatous cystitis were each documented in 1 case (12.5% each).

Cystitis cystica et glandularis, a benign entity that can masquerade as an invasive carcinoma, was identified in a 39-year-old male patient in this study. Histopathological assessment showed von Brunn nests invaginating from the surface epithelium. The cells appeared cuboidal to columnar, forming gland-like spaces, with some cystically dilated. No atypia, mitoses, stromal reaction, or muscle invasion was identified [Figure 4].

Malakoplakia, a rare and distinctive form of chronic cystitis, was identified in a 60-year-old female who presented with painless hematuria and increased urinary frequency. USG revealed polypoidal mass measuring 30X35mm in left lateral wall projecting into the bladder [Figure 5]. Contrast-enhanced CT revealed a poorly marginated, polypoidal, pedunculated growth arising from the lateral bladder wall [Figure 6]. Given the clinical presentation and radiological appearance, a neoplastic bladder lesion was suspected. On cystoscopy, a large nodular pedunculated mass was visualized arising from the Left lateral wall of the bladder [Figure7]. TURBT was done and the specimen was submitted to histopathology. Histopathological examination revealed sheets of histiocytes with granular eosinophilic cytoplasm with intracytoplasmic inclusions, identified as Michaelis–Gutmann bodies. These findings confirmed the diagnosis of Malakoplakia. Special stains confirmed the diagnosis: PAS and Von Kossa stains were positive [Figure 8] and cells were negative for Pan-CK and p63, excluding urothelial origin, and negative for S-100, ruling out a neural origin.

This study included 1 case of granulomatous cystitis secondary to BCG therapy. Histopathological examination revealed edema, fibrosis, and lymphocytic infiltration, with granulomas composed of histiocytes and epithelioid cells [Figure 3]. Intravesical administration of bacillus Calmette-Guerin for the treatment of urothelial carcinoma of the bladder can result in granulomatous inflammation. Nonetheless, tuberculosis remains the leading cause of granulomatous inflammation of the bladder [18].

The fifth edition of the WHO classification recognizes histological evaluation as the gold standard for diagnosing and classifying urothelial tract tumors [19, 23]. More than 95% of bladder carcinomas are of urothelial origin [13]. In our study, the most common neoplastic lesions were urothelial tumors (32 cases; 94.1%), followed by squamous cell carcinoma (1 case; 2.9%) and a mesenchymal tumor (1 case; 2.9%), findings comparable to those of Srikousthubha et al., who reported 96% urothelial carcinoma and 4% pure squamous cell carcinoma [22].

Non-invasive urothelial neoplasms constituted the majority (23 cases, 67.7%). Among these, PUNLMP accounted for 35.3%, non-invasive papillary urothelial carcinoma, low grade, for 23.6%, and non-invasive papillary urothelial carcinoma, high grade, for 8.8%. These findings differ from those of Singhal P et al., Suba G et al., and Agarwal S et al., who reported invasive papillary urothelial carcinoma as the most common subtype [7, 17, 20].

Histological grade and muscle invasion are the key prognostic factors in urothelial carcinoma [21]. The extent of invasion into the subepithelial connective tissue/lamina propria/submucosa has prognostic value in T1 disease [19]. Invasive urothelial carcinoma is notable for its morphological diversity, including squamoid, glandular, nested, trophoblastic, micropapillary, and plasmacytoid differentiation [17, 19]. Many of these variants have prognostic or therapeutic significance, making awareness of these patterns essential to avoid diagnostic errors [17].

Invasive urothelial neoplasm was seen in 9 cases (26.5%), of which 6 cases (17.7%) were invasive urothelial carcinoma, 2 cases (5.9%) with squamous differentiation and 1 case (2.9%) with poorly differentiated variant, slightly higher compared to Kundlia A, et al., [1]. High-grade was seen in 8 cases, and low-grade in 1 case. Lamina propria invasion was observed in all invasive urothelial carcinomas, whereas muscularis propria invasion (detrusor muscle) was observed in 4 cases of high-grade invasive urothelial carcinoma. In 2 cases, involvement of the muscularis propria could not be determined due to extensive cautery defects. The presence of muscle invasion strongly correlates with high-grade tumors, emphasizing the essential role of precise histopathological assessment in treatment planning and prognosis [1].

A case of embryonal rhabdomyosarcoma was reported in a 2-year-old male who presented with urinary difficulty and lower abdominal distension. Cystoscopy revealed a cystic lesion arising from the bladder neck. Histopathological examination showed primitive ovoid to spindle-shaped tumor cells with moderate pleomorphism and hyperchromatic nuclei, along with scattered rhabdomyoblast-like elongated cells and scattered atypical mitotic figures. Immunohistochemistry demonstrated positivity for SMA, Desmin, Myogenin, and MyoD1, confirming the diagnosis [Figure 12].

8. CONCLUSION

Urinary bladder lesions are diverse. Histopathological examination remains the gold standard for diagnosis, enabling distinction between neoplastic and non-neoplastic lesions, identification of benign mimickers, assessment of histological grade, and detection of muscle invasion, all of which are critical for guiding treatment and prognostication. Immunohistochemistry (IHC) serves as a valuable adjunct in cases with unusual histology or diagnostic uncertainty. A thorough understanding of the histological features, neoplastic potential, recurrence risk, and associated diagnostic challenges is essential for accurate diagnosis and optimal patient management

9. LIMITATIONS

As a single-center study, this study may not fully represent the epidemiological spectrum of urinary bladder lesions across various geographic regions and healthcare settings. The relatively small sample size limits the statistical power and generalizability of the findings. Additionally, the lack of long-term follow-up restricts the assessment of recurrence and survival outcomes, and advanced ancillary techniques such as immunohistochemistry or molecular profiling were not routinely employed, which could have provided deeper diagnostic insights.

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