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A Study of Histopathological Spectrum of Non Neoplastic Urothelial Lesions

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ABSTRACT

Background: Specimens from the bladder are commonly encountered by the general surgical pathologist. Emphasis is usually placed on the neoplasms of bladder, particularly if malignant, owing to their bad prognosis. A good command of benign lesions occurring in the bladder, and knowledge of their preneoplastic potential will help pathologists to confidently diagnose malignancy versus its benign mimickers and guide the urologists in choosing the appropriate therapy for the patient.

Aims & Objectives: To present a mixture of benign entities, and discuss their histologic characteristics, hoping to provide a practical review for the general surgical pathologist.

To discuss group of benign disorders that can cause diffuse bladder wall thickening and might be misdiagnosed as malignancy on cystoscopy.

Material and Methods: A retrospective study of 10 years was carried out on bladder biopsies received from Jan 2004 to Dec 2014 at a tertiary care hospital in mumbai. The histopathological records of patients were screened for collection of data like age, sex, clinical history, gross and microscopy. The final diagnosis was given on routine Hematoxylin & Eosin stained sections.

Results: Total 123 cases of non neoplastic bladder lesions were studied, out of which 69 were males and 54 were females with male to female ratio being 1.3:1.The spectrum of non neoplastic pathological lesions included cystitis, nephrogenic adenoma, BCG induced granuloma, malakoplakia and endometriosis. Cystitis was the most common finding. Most common age group affected by the non neoplastic lesions was 41-50 years of age.

Conclusion: A wide variety of benign entities are present in the bladder and are more commonly encountered by the general surgical pathologist. Knowledge of the histologic characteristics of these lesions, their preneoplastic potential, and the possible pitfalls can help the pathologist serve the patient better.

Key Words: Bladder, Benign, Cystitis, Histopathological spectrum, Non neoplastic

INTRODUCTION

Non-neoplastic urinary bladder lesions, are responsible for substantial morbidity throughout the world. The non-neoplastic lesions in particular cystitis comprise an imperative source of symptoms and signs. These diseases are considered more disabling than fatal. Precise diagnosis of urinary bladder lesions requires concurrent data from urology, radiology and surgical pathology. After cystoscopy, histopathology is considered as the primary diagnostic tool for patients who are suspected of having bladder tumours because there is direct light microscopic visualization of the bladder mucosa pathology. Emphasis is usually placed on the neoplasms of bladder, particularly if malignant, owing to their bad prognosis. A good command of benign lesions occurring in the bladder, and knowledge of their preneoplastic potential will help pathologists to confidently diagnose malignancy versus its benign mimickers and guide the urologists in choosing the appropriate therapy for the patient.

AIMS & OBJECTIVES

To present a mixture of benign entities, and discuss their histologic characteristics, hoping to provide a practical review for the general surgical pathologist.

To discuss group of benign disorders that can cause diffuse bladder wall thickening and might be misdiagnosed as malignancy on cystoscopy.

MATERIALS AND METHODS

A retrospective study was done over a period of ten years in the Department of Pathology, T.N.M.C & B.Y.L Nair Ch. Hospital, Mumbai from 1st Jan 2004 to 31st Dec 2014 and included 123 cases. The material for the study was comprised of biopsies from Transurethral resection of bladder tissue (TURBT). The biopsy specimens were received in 10% formalin. Data was collected in a preset performa. The histopathology records of patients were screened for collection of data like age, sex, clinical history, gross, microscopic findings and final diagnosis. All details of the patients were used anonymously and identity of the subject was not revealed anywhere in the study. The entire tissue was processed in all the cases. Routine processing was done starting from fixation, dehydration, embedding and section cutting. Staining was done by Hematoxylin and eosin . Histopathological examination of specimens was carried out and the lesions were classified into various types on light microscopy. Data was analyzed and tabulated for evaluation.

INCLUSION CRITERIA
- All the TURBT biopsies received in the Department of Pathology, T.N.M.C & B.Y.L. Nair Ch. Hospital, Mumbai from Jan 2004-Dec 2014.
- Adequacy of biopsy sample.

EXCLUSION CRITERIA
- Autolysed specimen
- Inadequate biopsies.
- All patients with incomplete data regarding clinical profile and histopathological reports were excluded from study.

RESULTS

A total of 123 urinary bladder biopsies were studied in a period 10 years. Hematuria was the most common clinical symptom in 28 cases followed by dysuria in 21 cases, increased frequency in 16 cases and burning micturition in 15 cases.

Age of the patients in our study ranged from 41 years to 80 years with a peak age incidence of 66 cases in the 4th decade followed by 35 cases in the 5th decade. Least number of cases were seen in 7th and 8th decade.

Males were more commonly affected than females. In the present study there were 69 male patients (56.1%) and 54 females (43.9%) with M:F ratio of 1.3:1.

Among the 123 cases of non-neoplastic lesions, majority were of papillary/polypoidal cystitis (35.77%). Other conditions in descending order were chronic non specific cystitis (23.58%), tubercular cystitis (17.8%), acute cystitis (10.57%), follicular cystitis (1.63%), acute on chronic cystitis (1.63%), nephrogenic adenoma (1.63%), BCG induced granuloma (1.63%), malackoplakia (0.82%), haemorrhagic cystitis (0.82%) and endometriosis (0.82%).

Table 1: Yearwise Distribution of Non Neoplastic Bladder Lesions

Year	Non Neoplastic Lesions
2004	11
2005	13
2006	14
2007	12
2008	9
2009	10
2010	6
2011	3
2012	16
2013	19
2014	10
TOTAL	123

Average non neoplastic cases were 10-20 per year.

Table 2: Age Distribution of Non Neoplastic Bladder Lesions

Age Group	Non Neoplastic Lesions	Percentage
41-50	66	53.65%
51-60	35	28.45%
61-70	21	17.1%
71-80	01	0.81%
TOTAL	123	100.0%

Non neoplastic lesions were most commonly seen in the 4th decade. Amongst the total 123 non neoplastic cases, 53.65% were seen in the 4th to 5th decade.

Table 3: Sex Distribution of Non Neoplastic Bladder Lesions

Sex	Non Neoplastic Lesions	Percentage
Female	54	43.9%
Male	69	56.1%
TOTAL	123	100.00%

Out of the 123 non neoplastic cases, 56.1% were males and 43.9% were females.

Table 4: Clinical Presentation of Non Neoplastic Bladder Lesions

Symptoms	Non Neoplastic Lesions
Hematuria	38
Dysuria	26
Frequency	21
Burning Micturition	19
Pain	10
Retention	8
Bladder Mass	1

Out of 123 non neoplastic lesions patients mostly presented with hematuria (38 cases), dysuria (26 cases), frequency (21 cases) and burning micturition (19 cases).

Table 5: Distribution of Non Neoplastic Lesions

Lesion	Count	Percentage
Paillary/Polypoidal Cystitis	44	35.77%
Tubercular Cystitis	22	17.8%
Acute Cystitis	13	10.57%
Chronic Non Specfic Cystitis	29	23.58%
Acute On Chronic Cystitis	2	1.63%
Follicular Cystitis	2	1.63%
Haemorrhagic Cystitis	1	0.82%
Cystitis Cystica/Cystitis Glandularis	4	3.3%
Endometriosis	1	0.82%
Malackoplakia	1	0.82%
Nephrogenic Adenoma	2	1.63%
Bcg Induced Granuloma	2	1.63%
Total	123	100%

Out of 123 non neoplastic cases, majority were of papillary / polypoidal cystitis (35.77%).Other conditions in descending order were chronic non specific cystitis(23.58%), tubercular cystitis(17.8%), acute cystitis(10.57%), follicular cystitis(1.63%), acute on chronic cystitis(1.63%), nephrogenic adenoma (1.63%), BCG induced granuloma (1.63%) , malackoplakia (0.82%), haemorrhagic cystitis (0.82%), and endometriosis (0.82%)

Table 6: Von Brunn's Nest Association

Von Brunn Nests	Frequency	Percentage
Present	18	14.6%
Absent	105	85.4%
Total	123	100.0%

Out of 88 cases of cystitis, 14.6% of the cases showed von Brunn's nests.

DISCUSSION

The term 'von Brunn's nests' refers to the presence of nests of transitional cells in the lamina propria, detached from the overlying urothelium. These nests arise by a process of invagination from the overlying urothelium and the term von Brunn's buds can be used when they are attached to the urothelium. It is the detachment from the overlying epithelium that can be problematic, particularly if the nests lie deeper in the lamina propria and are numerous.

Wiener et al and Volmar et al reported the occurrence of von Brunn nests in 89% of normal bladder mucosa. (1) (2). In our study, 14.6% of the cases of cystitis showed von Brunn's nests. Srikousthubha et al had also shown the association of von Brunn's nest with cystitis, which is in consonance with our observation (3). **(Table-6) (n=18) (FIGURE-1)**

Hameed and Humphrey reported cystitis cystica as a group of urothelial disorders featuring cystic cavities in the center of the von Brunn nests and dilated cystic cavities lining the true urothelium while the term cystitis glandularis was attributed to the glandular epithelium with mucosal cells mostly lining the cystic cavity, with cuboidal or columnar epithelium (4). In autopsy cases Harik and O' Toole reported cystitis cystica and glandularis in 60% of the normal bladder mucosa (5). Hameed and Humphrey emphasized that there is no relationship between the appearance of lesion in the bladder and the occurrence of bladder cancer (4).

In contrast to the typical form of cystitis glandularis, during the present study it was found that the cells lining the glands in the intestinal type cases were tall and columnar with abundant mucin. These cells were admixed with goblet cells and the epithelium resembled to that of the intestine. The two types of cystitis glandularis may coexist. In the present study, 3.3% cases of the non neoplastic lesions showed cystitis cystica and cystitis glandularis. **(n=4) (FIGURE-2,3 &4)**

Cystitis (91.8%) was documented as the most common non neoplastic lesion during the present study. There were cases of papillary polypoidal cystitis, tubercular cystitis, follicular cystitis, haemorrhagic cystitis and chronic non specific cystitis. In a study done in India by Kumar et al, 35% cases of cystitis were reported (6). Vaidya et al, in their study found 58.95% cases of chronic non specific cystitis (7). Srikoustubha et al in their study reported 25 non neoplastic cases and 21 cases (84%) of inflammatory lesions (3). Out of the 21 inflammatory lesions,15 cases (71.4%) were of polypoid chronic non specific cystitis, 3 cases (14.28%) were of tubercular cystitis and 1 case (4.76%) each of follicular cystitis, malackoplakia and squamous metaplasia. **(n=113)**

Papillary polypoidal cystitis refers to an exophytic, inflammatory lesion that occurs mostly due to the presence of indwelling catheters and is characterised histologically by normal to hyperplastic urothelium overlying a congested, chronically inflamed, and edematous stroma. Although these exophytic lesions grossly mimic a papillary neoplasm, they can be easily distinguished as an inflammatory pseudopolyp on microscopy. It usually arises when inflammation accompanied by edema leads to the papillae or polyp formation. The term papillary cystitis refers to when thin finger-like papillae are present, and polypoid cystitis when the lesions are edematous and broad based. Consistent with the several studies, our study encountered 44 cases (35.77%) of papillary polypoidal cystitis. Most of the cases had history of catheterisation and showed thickened bladder walls on sonography and congested mucosa on cystoscopy. Microscopically, lamina propria showed edema and chronic inflammatory cell infiltrate. **(n=44) (FIGURE-5,6)**

Another entity, tubercular cystitis was also encountered. The kidneys are the most common site of infection in genitourinary tuberculosis and are infected through hematogenous spread of the bacilli. Bladder lesions are without exeption secondary to renal tuberculosis. The diagnosis is based on culture studies by isolation of the causative organism, but biopsy occasionally may be required. In the present study all the 22 cases (17.8%) of tubercular cystitis showed the characteristic epithelioid cell granulomas, histiocytes, lymphocytes and langhan's type of giant cells. As many as 5 cases (4.1%) showed caseous necrosis. Vaidya et al, in their study found 0.93% cases of Tubercular cystitis (7). Appropriate stains should reveal the presence of acid-fast bacilli (8). **(n=22) (FIGURE-7)**

Another entity, follicular cystitis was used to describe the presence of lymphoid follicles with germinal centers in the wall of the urinary bladder (9). The term is a misnomer because it does not necessarily indicate inflammation. However, it does sometimes follow infection, repeated transurethral biopsies, or the instillation of intravesical chemoherapeutic agents or BCG. In the present study it was encountered in 1.63% cases of non neoplasic lesions. **(n=2) (FIGURE-8)**

Haemorrhagic cystitis which was known to occur from intravesical instillation of chemotherapeutic agents such as thiotepa and mitomycin C was also encountered. These agents induce cytologic atypia (which can be confused with CIS), including cytomegaly, pleomorphism, and hyperchromasia (10). These changes were limited to the superficial cells and mitotic activity was not evident. Microscopically, the bladder was characterized by marked edema and haemorrhage throughout the lamina propria, with ulceration and fibrinopurulent exudate. During the regenerative stage, macrophages and fibroblasts occupied the lamina propria, whereas the overlying epithelium exhibited an increased mitotic rate, increased thickness, and marked atypia (11) (12) . Presently it was diagnosed in 0.82% of the non neoplastic cases examined. **(n=1) (FIGURE-9)**

Malakoplakia, reported to be a rare chronic inflammatory disease ,was first described by Michaelis and Gutmann in 1902. It is known to have a female predominance with 50 years as an average age of presentation (13). From etiology point of view malakoplakia has been reported to represent a peculiar response to infection which has been attributed to disturbed immune response or abnormal macrophage or lysosomal activity in the host (14) (15). Its occurrence has been reported in the renal pelvis, ureter and urethera (16). In the present study, only one case (0.82%) of malakoplakia was encountered in a 45 years old female, which on microscopy showed Michaelis Gutmann bodies and numerous histiocytes infiltrating the lamina propria. **(n=1) (FIGURE-10)**

Nephrogenic adenoma , a metaplastic lesion was characterized by aggregates of cuboidal or hobnail cells with clear or eosinophilic cytoplasm and small nuclei without prominent nucleoli (17). These cells lined thin papillary fronds on the surface or formed tubular structures within the lamina propria of the bladder . It was fairly well circumscribed and did not extend into the muscularis propria. It was thought to result from an inflammatory insult or local injury (18). It was originally described in the trigone and given its name because it was thought to arise from mesonephric rests. This process has generally been thought to be metaplastic and the terms 'nephrogenic metaplasia' or adenomatous metaplasia' are preferred by some. Recently Mazal et al. studied cases of nephrogenic adenoma in kidney transplant recipients (19). Based on fluorescent *in situ* hybridization (FISH) and lectin studies, it was concluded that these lesions were derived from shed tubular cells originating from the transplanted kidney rather than a metaplastic process. Other authors have come to the same conclusion, based on other data, including the expression of PAX2 (20).

However several features of the tubular component of nephrogenic adenoma may pose particular diagnostic difficulty and merit emphasis. Tiny tubules containing mucin and apparently lined by a single cell with a compressed nucleus may simulate signet cells. The haphazard distribution of the tubules may simulate the appearance of invasive adenocarcinoma. Oliva and Young reviewed the microscopic appearances of 80 cases with unusual nephrogenic adenoma of the urinary tract . Only 2 cases (1.63%) were documented in the present study. **(n=2) (FIGURE-11)**

Urothelial carcinoma *in situ* (CIS) and high risk papillary carcinomas were commonly treated with intravesical installations of BCG which induced an intense inflammatory reaction (21). It was characterized by the presence of non caseating epithelioid cell granulomas and multinucleated giant cells. The granulomas were situated in the superficial third

of the lamina propria and were associated with an intense lymphocytic infiltrate. In the present study only 1.63% of the non neoplastic lesions were documented as BCG induced granulomas. **(n=2)**

Genitourinary involvement by endometriosis was seen in 1% to 2% of cases. More than 200 cases of vesical endometriosis have been described, making bladder the most common site of involvement within the urinary tract (22) . It affected women between the second and fifth decades of life, but rarely seen in postmenopausal women receiving exogenous estrogen . Interestingly, rare cases of vesical endometriosis have been reported in men with prostate carcinoma who were receiving exogenous estrogen therapy (23) (24). The occurrence in men most likely represented activation of müllerian rests by exogenous estrogens.

Clinically, patients presented with urgency, frequency, suprapubic pain, and rarely hematuria. A mass was frequently apparent either by palpation or cystoscopic examination (25) . Microscopically, the lesion resembled endometriosis elsewhere; endometrium-like glands seen in association with endometrial stromal cells and recent or old hemorrhage. Only 1 case of endometriosis was encountered during this study. **(n=1) (FIGURE-12).**

CONCLUSION

A wide variety of benign entities present in the bladder are more commonly encountered by the general surgical pathologist. Knowledge of the histologic characteristics of these lesions, their preneoplastic potential, and the possible pitfalls can help the pathologist serve the patient better.

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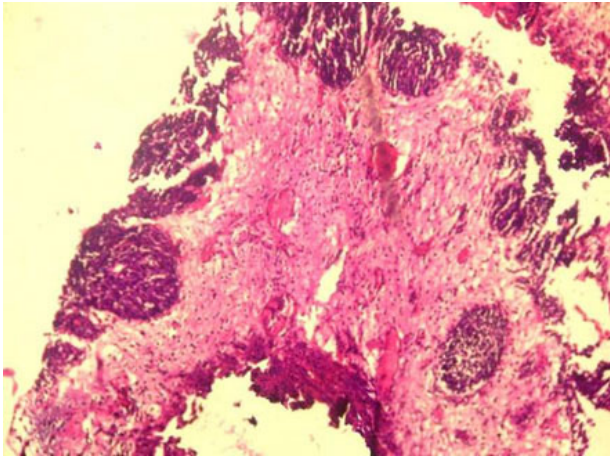

Figure 1: Von Brunn's Nests - section showing invagination of the benign surface urothelium into the underlying lamina propria. (H & E X 100).

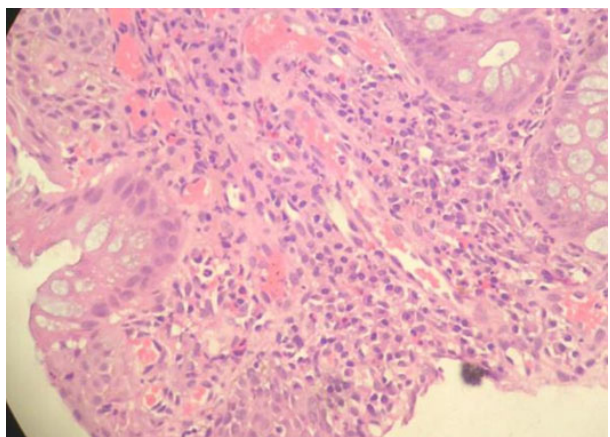**Figure 2:** Cystitis Cystica -section showing nests of benign appearing urothelium becoming cystically dilated. (H & E X 100).

Figure 3: Cystitis Glandularis- section shows urothelium undergone glandular metaplasia with intestinal type of epithelium and presence of goblet cells (H & E X 100) 400).
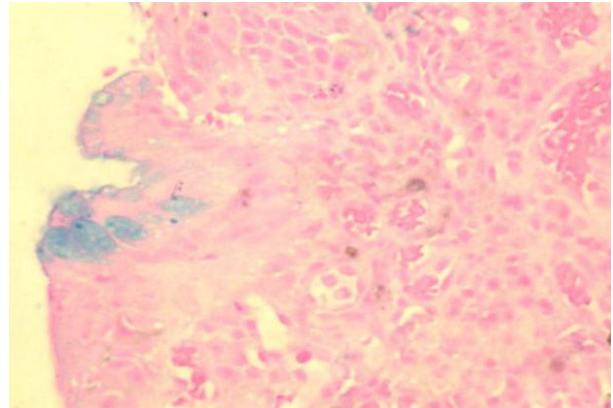
Figure 4: Cystitis Glandularis -goblet cells are stained blue hence positive for alcian blue. (special stain Alcian Blue).
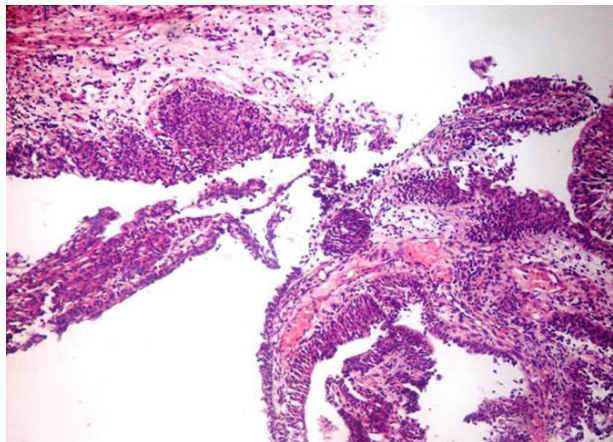
Figure 5: Papillary/Polypoidal Cystitis-section shows papillary configuration of the urothelium with lamina propria showing inflammation. (H & E X 100).
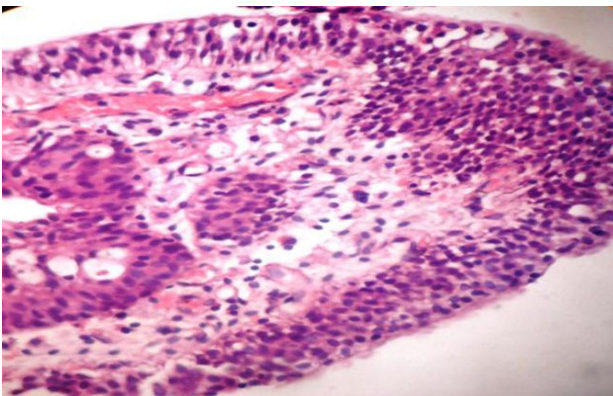
Figure 6: Papillary / Polypoidal Cystitis- section shows polypoidal hyperplastic urothelium overlying a congested, chronically inflamed edematous stroma. (H & E X 100_)
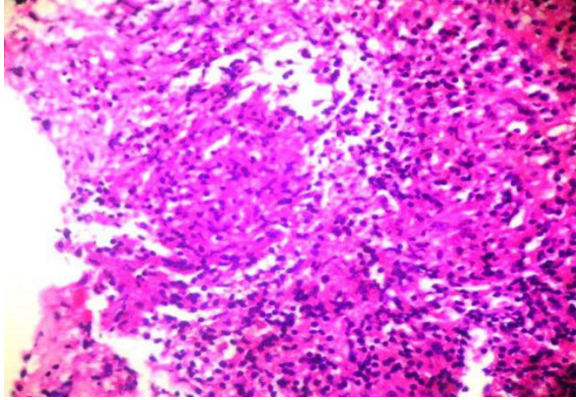
Figure 7: Tuberculous Cystitis- section shows ulceration of the urothelium with caseating epithelioid cell granulomas, langhans giant cells and chronic inflammatory infiltrate in the lamina propria. (H & E X 100).
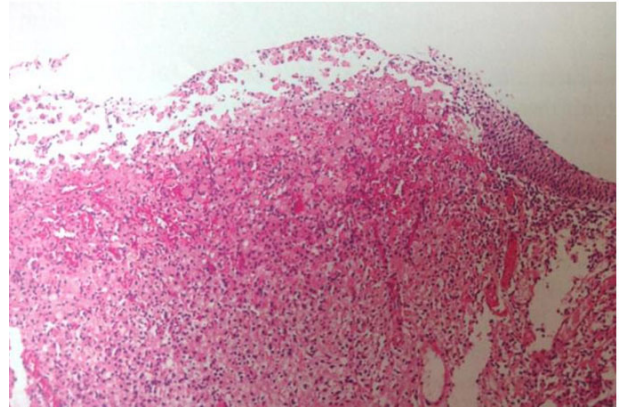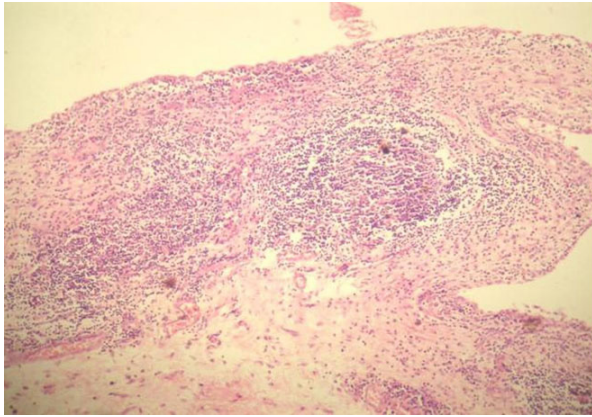

Figure 8: Follicular Cystitis - section shows presence of lymphoid follicles with germinal centres in the wall of urinary bladder. (H & E X 100).

Figure 9: Haemorrhagic Cystitis- section showing ulcerated and thinned surface urothelium with haemorrhage, edema and inflammation in the lamina propria. (H & E X 100).

Figure 10: Malakoplakia- section shows thinned denuded urothelium with lamina propria densely infiltrated by histiocytes. (H & E X 100).
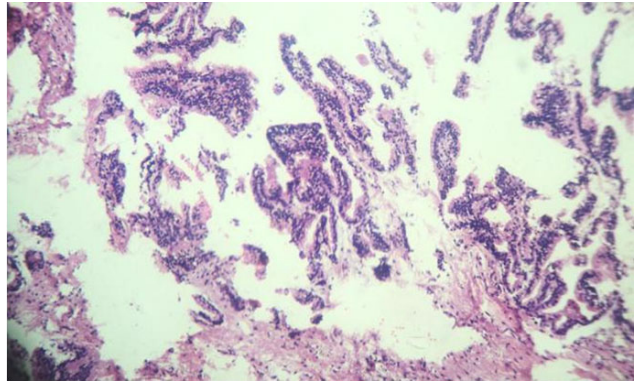

Figure 11: Nephrogenic Adenoma- section shows a proliferative urothelial lesion characterised by aggregates of cuboidal cells with scant eosinophilic cytoplasm forming tubules within the lamina propria (H & E X 100).
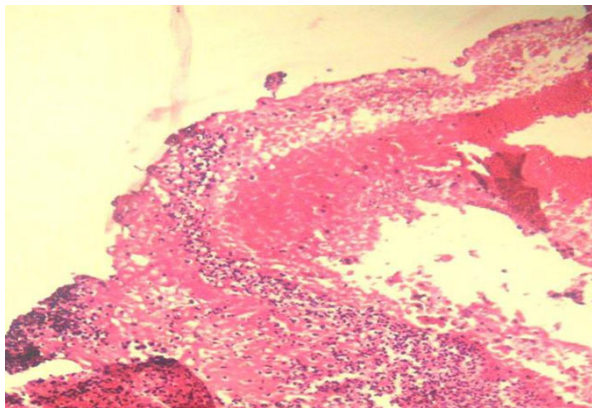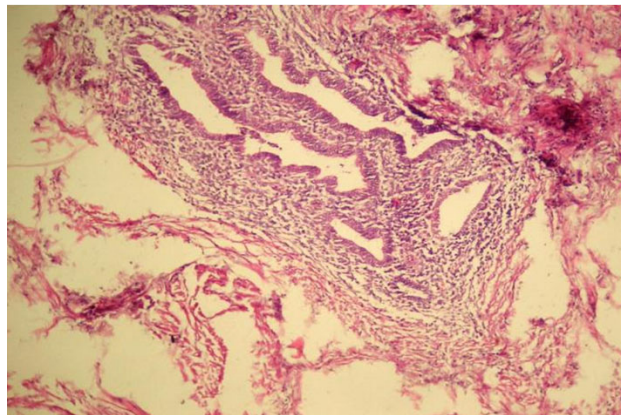

Figure 12: Endometriosis - section shows endometrial glands and endometrial stroma in the muscle wall of the bladder. (H & E X 100).