International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2021; 4(1): 28-35
Received: 16-11-2020
Accepted: 18-12-2020

Sarita Devdhar
Associate Professor, Noida International Institute of Medical Sciences, Greater Noida, Uttar Pradesh, India

Pallavi Sharma
Assistant Professor, G.S Medical College, Pilkhuwa, Uttar Pradesh, India

Jyoti Mishra
Associate Professor, School of Medical Sciences and Research, Sharda University, 32,34 Knowledge Park III, Greater Noida, Uttar Pradesh, India

Dr. Dushyant Sharma
Professor, Department of Pathology, G.S Medical College, Pilkhuwa, Uttar Pradesh, India

Dr. Sumit Giri
Professor, Department of Pathology, G.S Medical College, Pilkhuwa, Uttar Pradesh, India

Corresponding Author:
Pallavi Sharma
Assistant Professor, G.S Medical College, Pilkhuwa, Uttar Pradesh, India

Histomorphological evaluation of non-neoplastic lesions of the urinary bladder

Sarita Devdhar, Pallavi Sharma, Jyoti Mishra, Dr. Dushyant Sharma and Dr. Sumit Giri

DOI: https://doi.org/10.33545/pathol.2021.v4.i1a.321

Abstract
Aim: The aim of this study is to evaluate the urinary bladder biopsies for non-neoplastic lesions.
Materials and Methods: This study includes 41 non-neoplastic bladder lesion cases out of 125 urinary bladder samples received by histopathology laboratories of two medical colleges between October 2017 and January 2020. The samples included transurethral tumor resections and bladder biopsies.
Results: In the present study, seventy-two (59%) cases had neoplastic lesions, 29 (24%) cases had non-neoplastic lesions and 12 (10%) cases showed neoplastic in association with non-neoplastic lesions. The most common non-neoplastic lesions encountered were follicular cystitis, chronic cystitis, and hemorrhagic cystitis.
Conclusion: In symptomatic lower urinary tract disease, cystoscopy and histopathological evaluation is rewarding in the diagnosis of various non-neoplastic causative lesions. Awareness of these entities facilitates easy diagnosis and differentiation from malignant processes.

Keywords: histomorphological, non-neoplastic lesions, urinary bladder

Introduction
Specimens from the urinary bladder are fairly commonly encountered in the histopathology laboratory. Emphasis is usually placed on neoplasms. A good command of benign lesions occurring in the bladder and knowledge of their preneoplastic potential will help pathologists accurately diagnose malignancy and guide management [1].

Materials and Methods
This study includes 41 non-neoplastic bladder lesion cases out of 125 urinary bladder samples received by histopathology laboratories of two medical colleges between October 2017 and January 2020. The samples included transurethral tumor resections and bladder biopsies. Cases which were diagnosed with non-neoplastic conditions of the urinary bladder, either singly or in association with neoplastic disease were included in the study. Specimens for histopathological examination were received in 10% formalin and the tissue was processed by routine paraffin embedding technique. The sections were stained with Haematoxylin and Eosin stain and a detailed microscopic examination was done. Relevant details pertaining to these cases i.e. presenting symptoms, imaging and cystoscopy findings were retrieved from the patient files and histopathology requisition forms, whenever available.

Results and Analysis
In the present study, seventy-two (59%) cases had neoplastic lesions, 29 (24%) cases had non-neoplastic lesions and 12 (10%) cases showed neoplastic in association with non-neoplastic lesions. Nine (7%) cases showed normal histology and three specimens were inadequate for opinion.

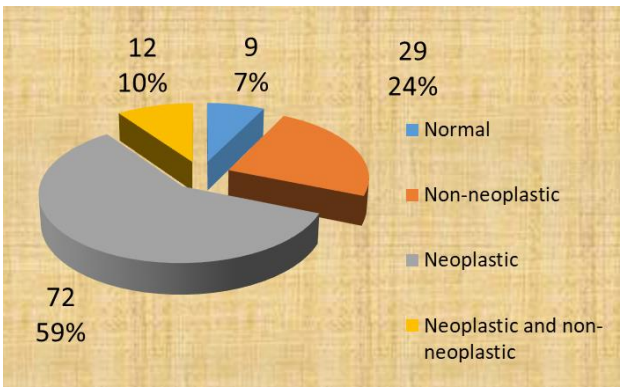

Fig 1: Types of lesions encountered in urinary bladder biopsies

Table 1: Age distribution of patients with non-neoplastic lesions

Age intervals	No. of patients
0-10	0
11-20	0
21-30	3
31-40	5
41-50	9
51-60	10
61-70	6
71-80	6
81-90	1
91-100	0
Age not mentioned	1

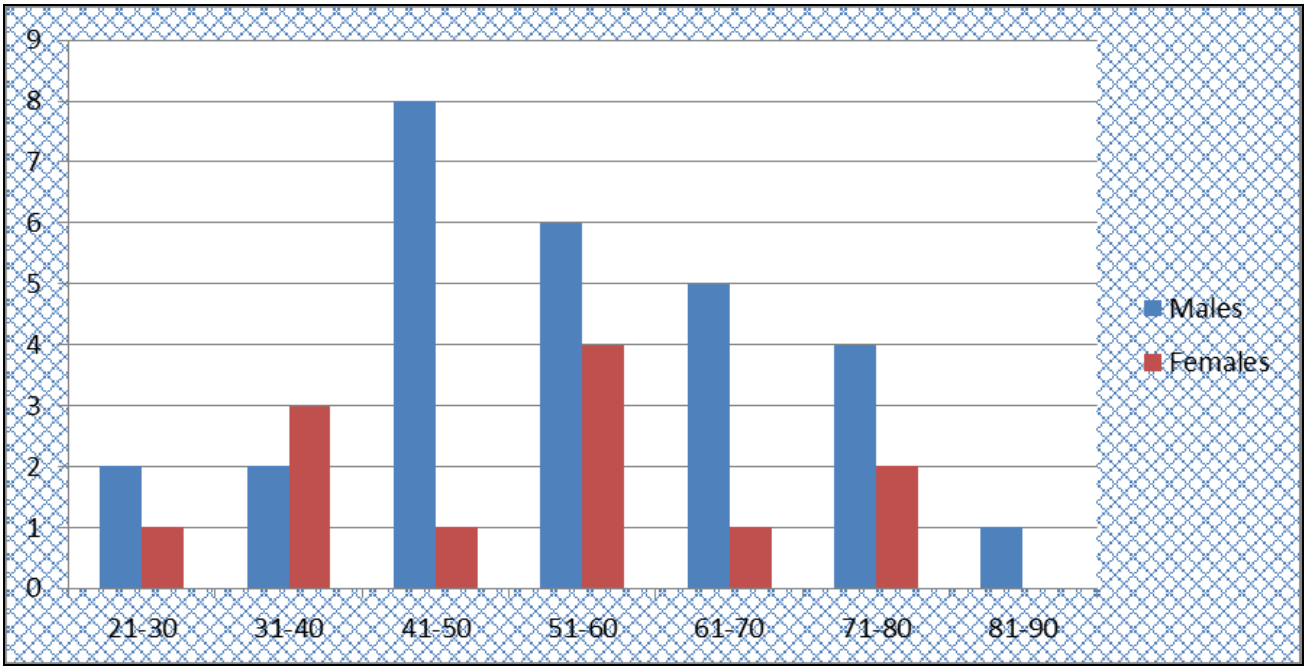

Fig 2: Age and sex distribution of non-neoplastic lesions

Table 2: The presenting symptoms of 29 cases of non-neoplastic urothelial lesions

Symptoms	No. of cases
Hematuria	20
LUTS*	25
Difficulty in micturition	11
Loin pain	3
No symptoms/ incidental finding	14

*LUTS (Lower Urinary Tract Symptoms) – includes dysuria, frequency of micturition, and burning micturition)

Table 3: The types of non-neoplastic lesions of the urinary bladder

Type of lesion	No. of cases
Chronic cystitis	13
Acute cystitis	2
Haemorrhagic cystitis	5
Follicular cystitis	15
Tuberculous cystitis	1
Eosinophilic cystitis	2
Polypoid cystitis	1
Diverticulum associated cystitis	1
Cystitis cystica	1
Urothelial hyperplasia	1

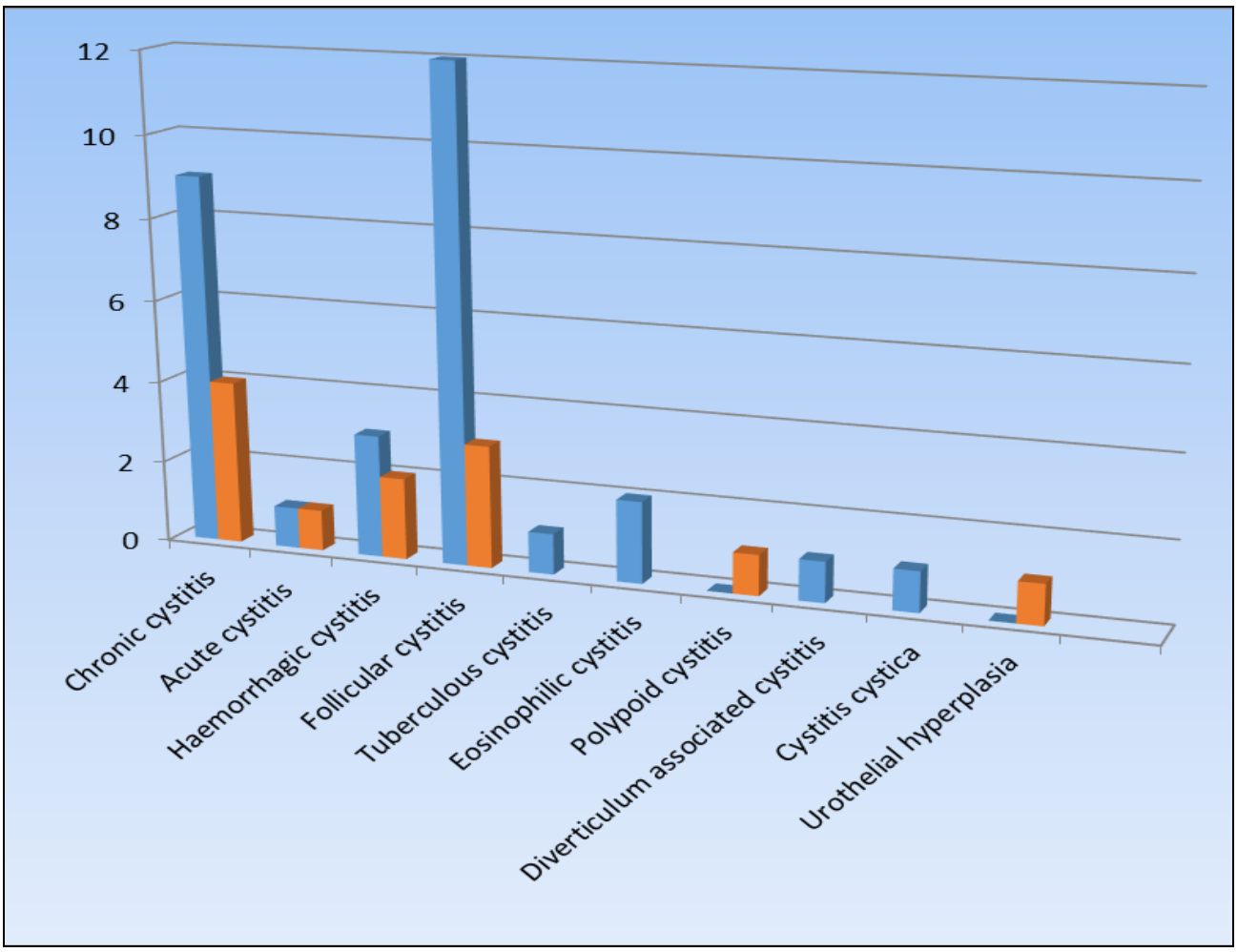

Fig 3: Various non-neoplastic lesions seen in our study

The mean age among patients with non-neoplastic lesions of the urinary bladder was found to be 52.6 years. Twenty eight patients were male, and 12 were female, the gender ratio being 2.3:1. Most patients presented with LUTS (Lower Urinary Tract Symptoms) – includes dysuria, frequency of micturition, and burning micturition) and hematuria. The commonest non-neoplastic lesions encountered were follicular cystitis, chronic cystitis, and hemorrhagic cystitis. It has been observed that these non-neoplastic lesions were more common in the males in all the age groups, except in the 31-40 years group where they were more common in females. The incidence of cystitis increased in males in the 40-70 age group.

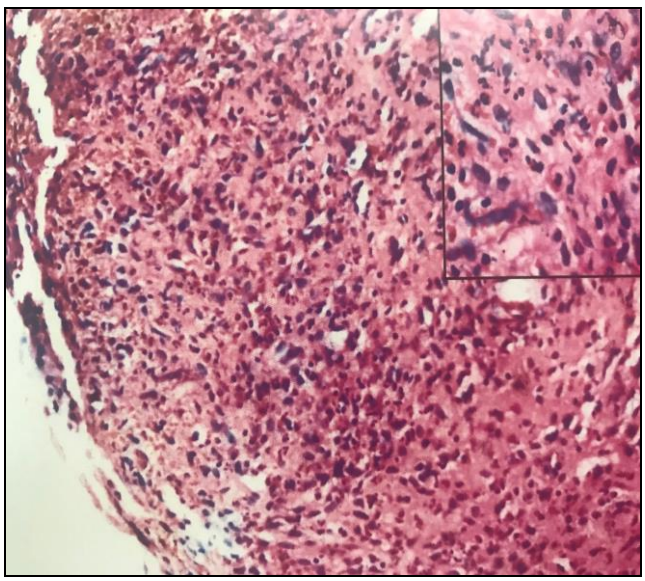

Fig 4: Acute cystitis (H&E X100). Inset(H&E X 400)

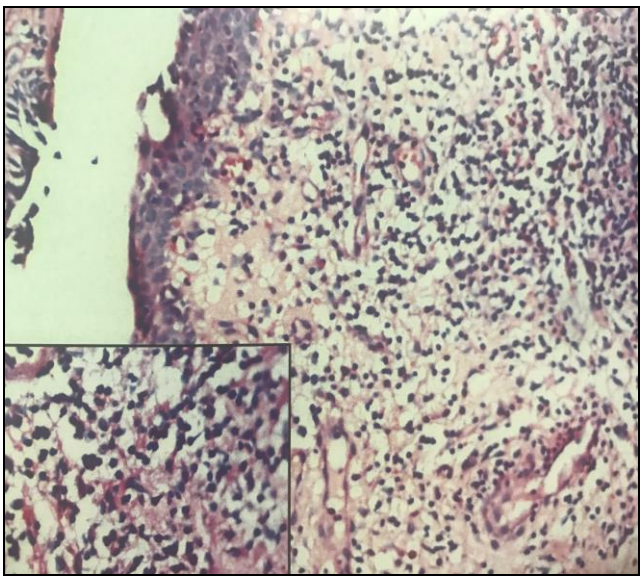

Fig 5: Chronic Cystitis: (H&E X 100) Inset (H&E X 400)

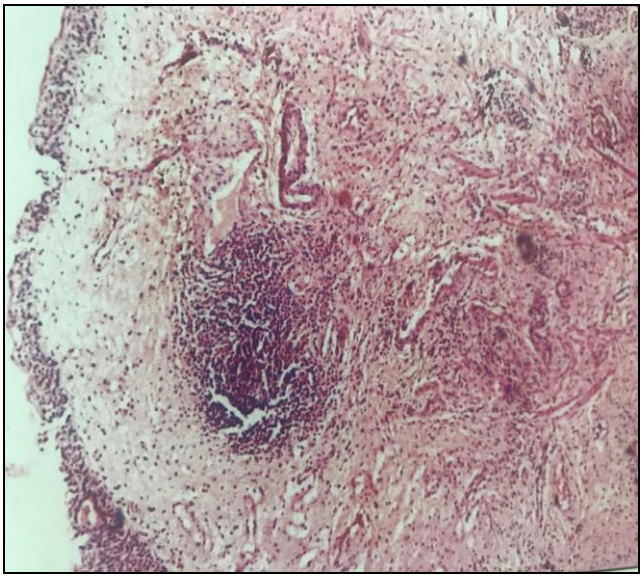

Fig 6: Follicular Cystitis (H&E 40)

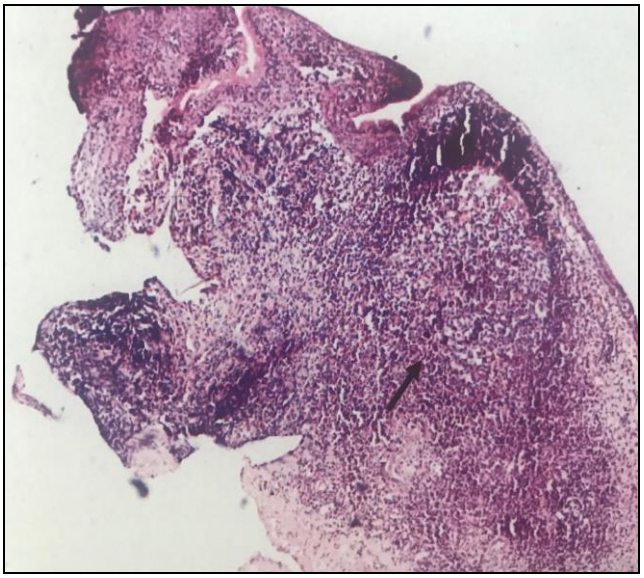

Fig 7: Follicular Cystitis showing lymphoid folloicles with germinal centres. (H&E 400)

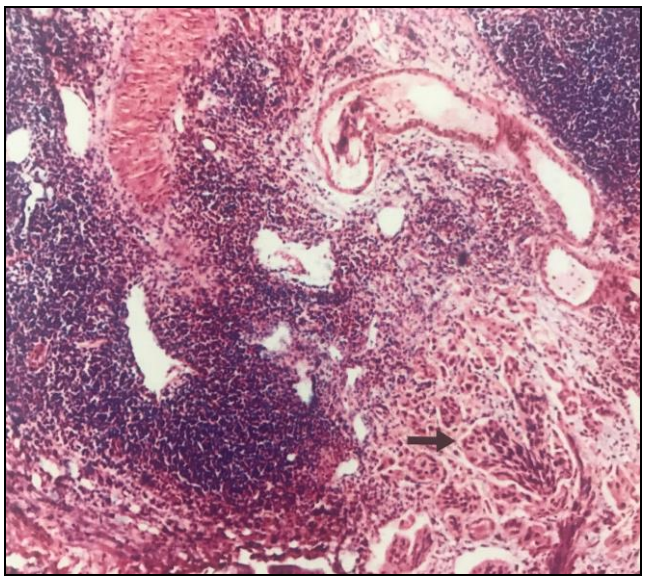

Fig 8: Follicular Cystitis along with arrow showing infiltrating carcinoma.(H&E X 40)

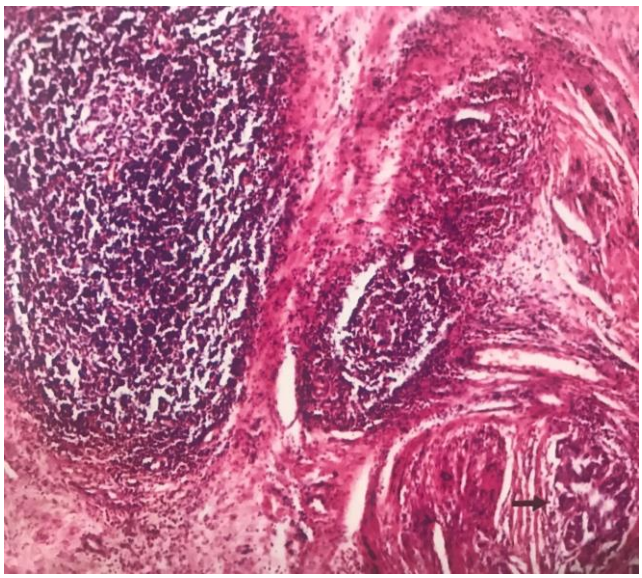

Fig 9: Follicular Cystitis along with arrow showing infiltrating carcinoma. (H&E X 100)

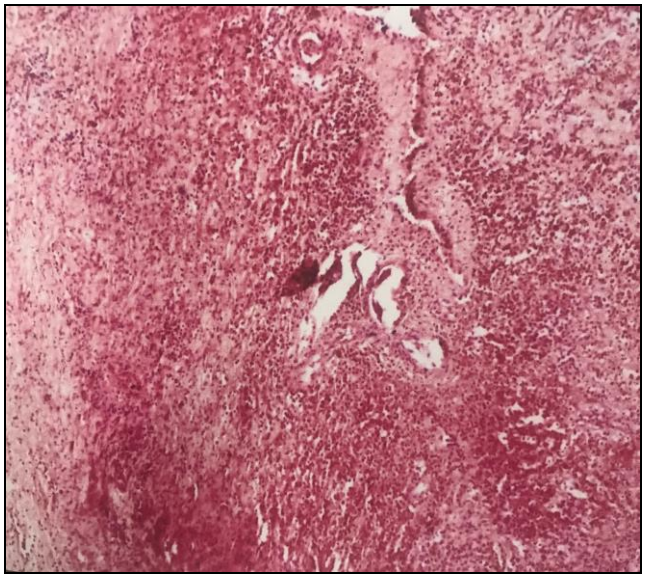

Fig 10: Eosinophilic Cystitis (H&E X 40)

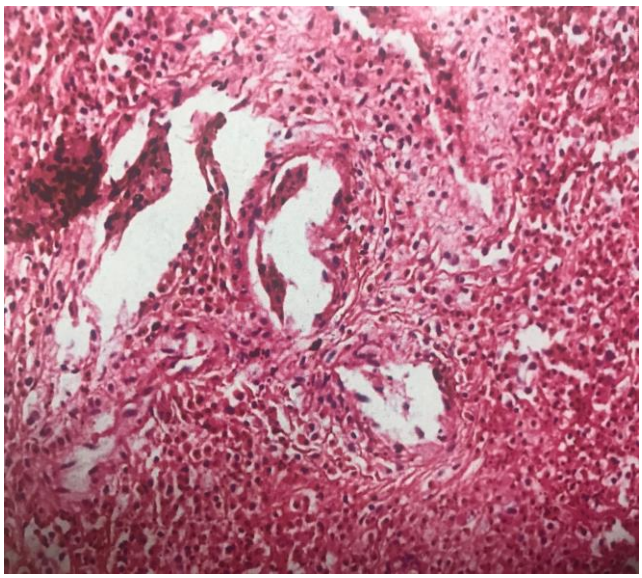

Fig 11: Eosinophilic cystitis (H&E 100)

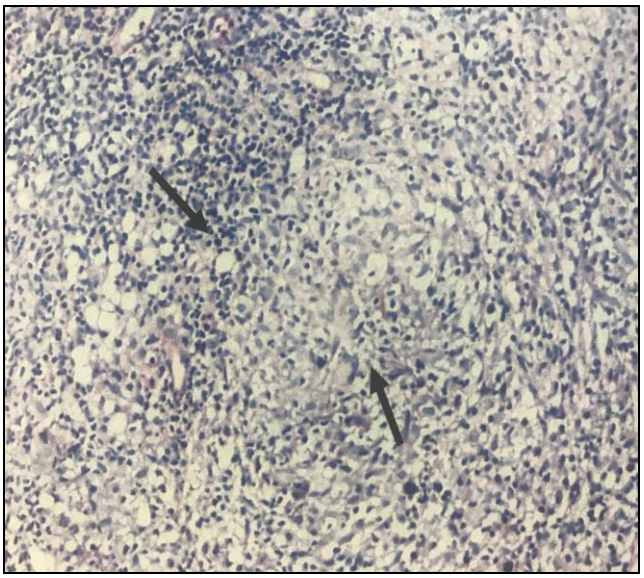

Fig 12: Tuberculous Cystitis with arrow showing granuloma (H&E - 100)

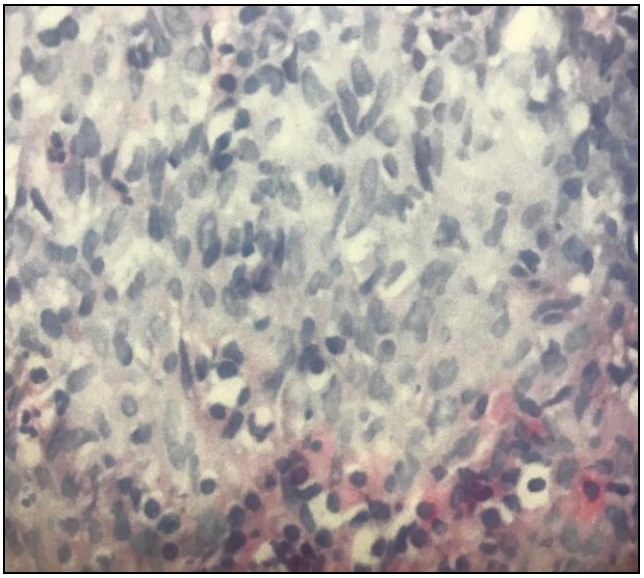

Fig 13: Tuberculous Cystitis showing granuloma composed of epithelioid cells. (H&E-400)

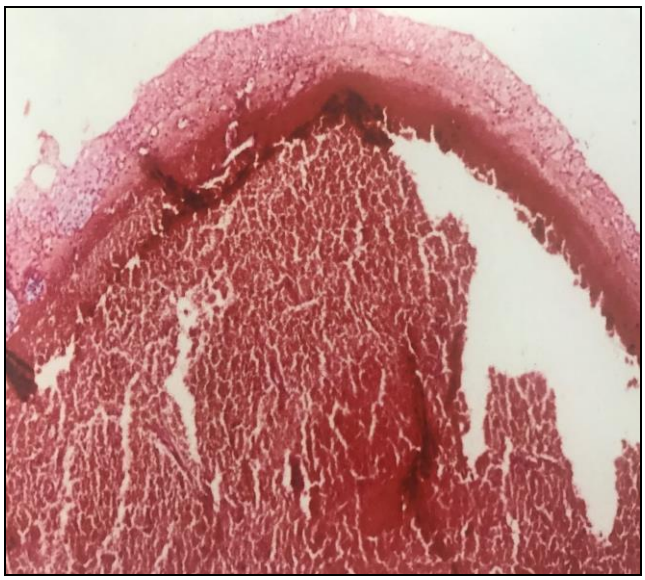

Fig 14: Hemorrhagic Cystitis: (H&E - 40 X)

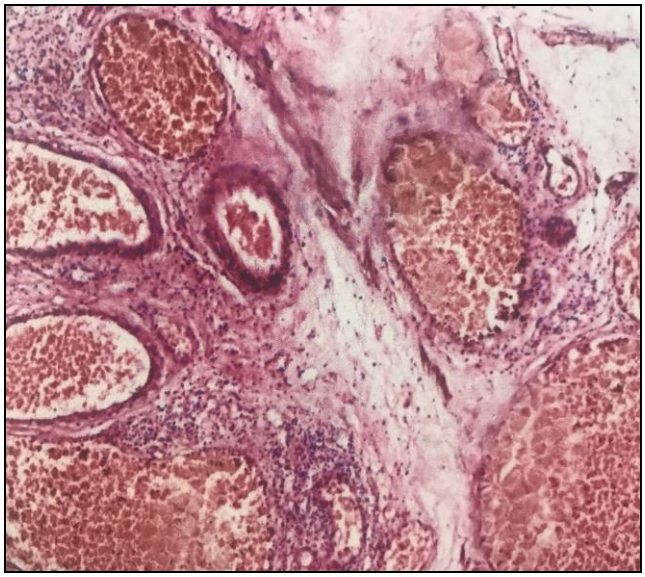

Fig 15: Hemorrhagic Cystitis (H&E - 100X)

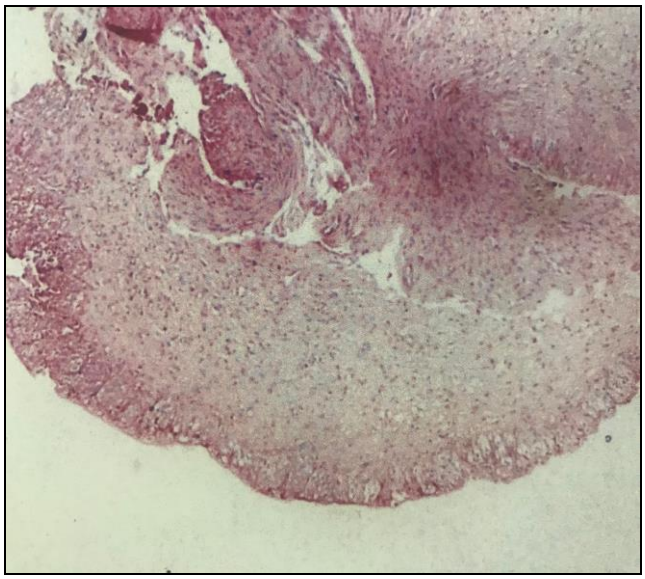

Fig 16: Polypoid Cystitis (H&E X 40)

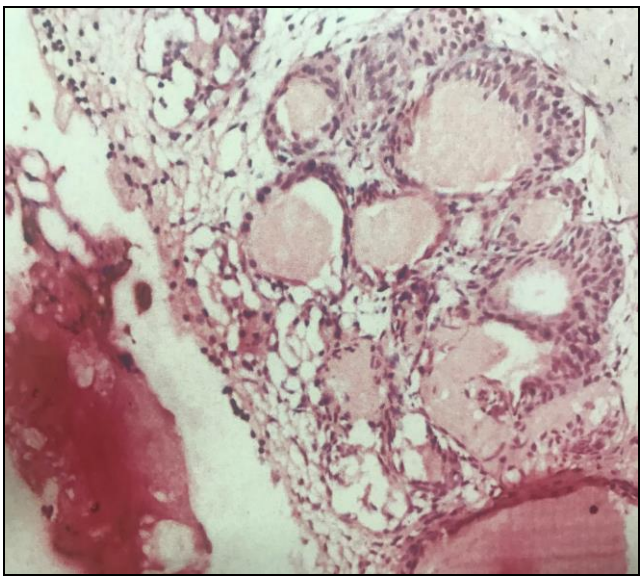

Fig 17: Cystitis Cystica (H&E x 40)

Discussion

Majority of the non-neoplastic lesions of urinary bladder consist of the various forms of cystitis. Cystitis may be broadly defined as any inflammatory condition that affects the urinary bladder. It is only rarely associated with mortality, usually in cases with urosepsis. On the other hand, it is the cause of morbidity, particularly in women. At one end of the spectrum are brief and self-limited, albeit painful attacks of acute cystitis from which an estimated 10 to 20 percent of women suffer at some point during their lifetime. At the other end of the spectrum are intractable and indeterminable cases of interstitial cystitis, which seems, for the patient at least, to go on for decades [2].

In the present study, seventy-two (59%) cases had neoplastic lesions, 29 (24%) cases had non-neoplastic lesions and 12 (10%) cases showed neoplastic in association with non-neoplastic lesions. In the study by Shreshtha EP *et al.* [3], out of 53 cases, 42(79%) were neoplastic and 11(21%) cases were non neoplastic lesions.

Similarly, 41.67% non-neoplastic and 58.33% neoplastic lesions were reported among urinary bladder lesions by Sushmitha S and co-workers [4].

Goyal VK [5] *et al*. reported inflammatory lesions in the range of 4% while carcinoma was present in 96% patients in their study.

It is quite evident that in the urinary bladder biopsies, neoplastic lesions outnumber non-neoplastic diagnoses. Neoplastic lesions, when suspected on cystoscopy, more often warrant biopsies as compared to the non-neoplastic lesions, which might be treated medically most of the times. It is when there is diagnostic confusion with malignant processes clinically or cystoscopy wise, a biopsy is mostly resorted to.

The commonest non-neoplastic lesions encountered in our study were follicular cystitis (15 of 42 cases, chronic cystitis (13 of 42 cases) and hemorrhagic cystitis. In the study by Shreshtha EP *et al* [3], among 11 non-neoplastic lesions, 3 cases were ulcerative polypoid cystitis, 3 were chronic cystitis, 2 were cystitis glandularis and 3 were granulomatous cystitis. We had one case of polypoid cystitis, one biopsy with tuberculous cystitis and one showing cystitis cystica.

In the study by Sushmitha S *et al.* [4], chronic nonspecific cystitis was the predominant type constituting up to 60% of all non-neoplastic lesions. Other types of cystitis studied were one case each of granulomatous, acute on chronic, polypoidal, eosinophilic and follicular cystitis.

In the study by Goyal VK *et al.* [5], chronic non-specific cystitis was the most common non-neoplastic lesion, along with few cases of eosinophilic cystitis. Most studies hence found chronic cystitis to be the common benign lesion in urinary bladder biopsies, whereas we found follicular cystitis to be the most frequent. The reason could be arbitrarily defined criteria for labelling a cystitis as non-specific or follicular [6] The diagnosis of follicular cystitis rests on the microscopic identification of lymphoid follicles with germinal centres located in the lamina propria of the bladder [7].s

In our study, we found 15 cases of follicular cystitis. These follicles had well-defined germinal centres with mantle zones. The density of follicles varied from case to case. The lamina propria showed dense chronic inflammatory infiltrate even between the follicles.

12 patients who were diagnosed with follicular cystitis in our study were males, and 3 were females; 11 of them were associated with bladder carcinoma. The age ranged between 48-60 years. These findings might be attributable to the obstructive prostatic hyperplasia related symptoms in older men, which was contributory to the development of follicular cystitis. Follicular cystitis most commonly occurs in a setting of chronic infection secondary to instrumentation or obstruction [7]. Cystoscopically, follicular cystitis is detected as pin-point white nodules, often on an erythematous mucosa [6]. In our study of cases with follicular cystitis - hyperemia, inflammation and bladder wall thickening were the common findings on cystoscopy.

In the present study 12 (10%) cases showed neoplastic lesions in association with non-neoplastic lesions. Follicular cystitis was the lesion most commonly encountered in association with bladder neoplasms in our study, 11 cases of which were associated with bladder carcinoma. Chronic inflammation is thought to have a role in the pathogenesis of urothelial carcinoma. This association is well established in the pathogenesis of squamous cell carcinoma of the bladder subsequent to schistosomiasis infection [1].

For instance, the association of lymphoid follicles with bladder neoplasms has been found strong [7]. Follicular cystitis occurs in upto 40% of patients with bladder carcinoma [8]. Sarma [9] found nodular lymphoid collections with germinal centres in 91 of 230 patients with bladder carcinoma in the mucosa away from the tumor. Other authors have described it in association with CIS. This fact was supported by the findings in our study too.

It has been observed that these non-neoplastic lesions were more common in the males in all the age groups, except in the 31-40 years group where they were more common in females. This may be because of increased frequency of infections in women in the reproductive age group. The incidence of cystitis increased in the males in 40-70 age group, probably due to the higher incidence of prostatic hyperplasia and bladder neck obstruction. In the study by Sushmitha *et al.* [4], however, such a male preponderance in the middle-elderly age was not brought out, nor was a female susceptibility in the reproductive age group; possibly due to the smaller numbers of non-neoplastic lesions assessed in their study.

Repeated or persistent attacks of acute cystitis result in chronic inflammatory changes. At gross examination, the bladder shows thickening of the wall and a variegated

mucosal surface [10] The typical case occurs in a middle-aged adult woman, but the lesion has been observed in adult men and uncommonly, even in children. The most common symptoms are suprapubic pain, frequency, urgency, nocturia, with or without hematuria. At cystoscopy, the bladder mucosa may be initially normal and without glomerulations or terminal hematuria, but subsequent examination with hydrodistension may show the typical features. These lesions are most prevalent in the dome, posterior wall, and lateral walls and are only rarely present in the trigone region. The negative urine cultures are both characteristic and confounding. Various forms of therapy have been entirely unsatisfactory. Microscopically, the mucosa may be normal or show non-specific proliferative changes, such as Von Brunn nests and cystitis cystica. Ulcers may be absent, especially in early cases. When present, they are non-specific with typical acute inflammatory reactive changes in the ulcer crater. The mere presence of urothelial ulcers does not by itself justify the diagnosis of chronic interstitial cystitis. The predominant findings in the lamina propria are vascular dilatation, marked stromal edema and a variably dense chronic inflammatory infiltrate. These changes are most marked in the lamina propria. A useful microscopic feature is the presence of mucosal tears with fibrin and erythrocytes, corresponding to granulations seen cystoscopically. The cell infiltrate is composed primarily of lymphocytes and plasma cells, with fewer neutrophils and mast cells, and inconstant eosinophils and histiocytes. Statistically increased numbers of mast cells have been reported in the muscularis propria layer in cases of interstitial cystitis compared with other types of cystitis. This layer also shows edema, chronic inflammatory infiltrate and commonly fibrosis [7]. This was the most common form of cystitis encountered in the present study (n=13), nine males and four females. The patients presented with hematuria, dysuria, and low back pain. Cystoscopically, bladder inflammation was found in most of the cases, with one case showing a white patch near the trigone.

Acute cystitis represents a bacterial infection of the bladder with the classic clinical signs of dysuria, urgency, and frequency, in the absence of systemic symptoms. Females suffer most urinary tract infections during the childhood and childbearing years. Urinary tract infections in men are rare before age 50 but increases beyond that age due to increasing prostatism [10]. In our study, there were two cases of acute cystitis, both being males. They presented with hematuria, and LUTS. One patient was a 68 year old, who presented with hematuria, burning micturition, and urinary retention of one week duration. The other patient was a 66 year old male patient who had associated hemorrhagic cystitis. The findings in our study reiterate that urinary tract infections in males are seen in the older sub-group.

Cystitis with a predominantly hemorrhagic clinical presentation may be caused by chemical toxins, radiation, viral infection, or may be idiopathic [8]. Since its introduction, cyclophosphamide has been recognized as a potent bladder toxin associated with hemorrhagic cystitis. Microscopically, the bladder is characterized by marked edema and hemorrhage throughout the lamina propria, with extensive ulceration and an associated fibrinopurulent exudate. During the regenerative stage, macrophages and fibroblasts populate the lamina propria while the overlying epithelium exhibits an increased mitotic rate, increased thickness, and marked atypia. At this stage, it can be confused with CIS, but despite these changes, mitotic activity is not evident and umbrella cells are preferentially affected [11]. Five cases of hemorrhagic cystitis were found in our study, 3 were males, and 2 were females. Hematuria, dysuria and fever were the common symptoms. One of these was a case of carcinoma cervix. Cystoscopically, areas of congestion, intense cystitis with 'velvety red interior', and thickened wall were the common findings. Accurate history regarding drug administration could not be sought. In one case, intense hemorrhage was seen in association with acute cystitis. In this case, ultrasonography showed an irregularly thickened bladder wall suggestive of hemorrhagic cystitis or urothelial carcinoma. Cystoscopy had also showed multiple solid tumor lesions diffusely laid in the bladder, and clinically it had been suspected to be a high grade urothelial carcinoma.

Eosinophilic cystitis is regarded as an allergic reaction involving the bladder mucosa. Associated peripheral eosinophilia may be present. The diagnosis requires close correlation of clinical and pathologic features; based on the cumulative evidence of sterile urine cultures, prominence of eosinophils and response to anti-histaminic and corticosteroid therapy in some patients. The identical lesion can be observed in elderly male patients with bladder outlet obstruction, frequently with a history of previous surgical therapy, and in patients with urothelial carcinoma. The disease is most common in middle-aged adults. Patients present with dysuria, frequency, and less commonly, hematuria. The bladder appears inflamed at cystoscopy, but has no features specific for this form of cystitis [7]. In the study by Verhagen, Nikkels, and Jong [12], the complaints of patients included urgency, frequency, abdominal pain, and hematuria. In three patients, the symptoms and ultrasound pictures suggested a bladder tumor. Microscopically, there is a dense transmural infiltrate of eosinophils with variable associated stromal edema and fibrosis [8]. In our study, we got 2 cases showing eosinophilic cystitis, both males, aged 45 and 55 years, respectively. One of the patients presented with bladder outlet obstruction, ultrasonography showed a bladder outgrowth in the anterior and right lateral wall (2.7 X 1.7 cm) with urinary bladder wall thickening (5.6 mm) and cystoscopy showed a mass like lesion in the bladder neck. The other patient presented with hematuria and LUTS.

In cases with genitourinary tuberculosis, about 61% show renal involvement, 19% involve the ureter, and the bladder is less frequently affected. Tuberculosis of the genito-urinary tract usually occurs 5-20 years after a primary lesion that is often in the lung. Hematogenous spread of tubercle bacilli seeds the kidney causing a granulomatous reaction. Less frequently, tuberculous cystitis is secondary to spread from a hematogenously infected prostate, seminal vesicles, or epididymis [10]. Most tuberculous bladder lesions are caused by Mycobacterium tuberculosis secondary to renal involvement [11]. Frequency, urgency, hematuria, and dysuria are the common symptoms [7]. Cystoscopically, the ureteral orifices are often hyperemic during the active phase of the disease, and delta-shaped patches of redness are apparent beneath the orifice. Bladder exudates, and single or multiple ulcerations may be observed. If the disease is long-standing fibrosis and contracture of the vesical wall may be appreciated on gross examination, resulting in a low-capacity bladder. Microscopically, caseating granulomas consisting of epithelioid histiocytes and giant cells surrounding central necrosis form in the submucosa with subsequent ulceration of the overlying mucosa. The

diagnosis of tuberculous cystitis is confirmed by a positive tissue acid-fast stain and culture [10]. The histology of granulomatous cystitis more typically seen in current practice is that associated with intravesical bacillus Calmette-Guerin (BCG) immunotherapy for superficial bladder cancer and consists of small, non-caseating granulomas limited to the superficial lamina propria, and acid-fast stains only rarely demonstrate organisms [11]. We encountered one case of a 41 year old male, who presented with terminal dysuria, pain in the perineum, and post-ejaculatory pain. Cystoscopically, diffuse tubercles with complete 'redout' of the mucosa was seen. Urine was positive for AFB on culture. Microscopically, well-formed granulomas were seen, with positivity for AFB by Ziehl-Neelsen stain.

Papillary, polypoid, and bullous cystitis are inflammatory lesions of the bladder mucosa characterized by exophytic mucosal projections. Histologically, they are associated with vascular congestion, stromal edema, and sometimes, an inflammatory cell infiltrate involving the lamina propria. The terms papillary, polypoid, and bullous are accurately descriptive of the gross morphologic characteristics of the exophytic lesions. It occurs equally in males and females, with an age range of 20 months to 79 years [7]. Polypoid cystitis is present in upto 80% of patients with indwelling catheters, and are referred to by urologists as 'catheter cystitis'. It is a benign lesion without any risk of developing into a carcinoma, but papillary and polypoid cystitis must be distinguished from papillary urothelial carcinoma. In our study, we found a case of polypoid cystitis in a 27 year-old female who presented with irritative symptoms, and on cystoscopy showed a 'growth' in the anterior wall. Histologically, it proved to be a polypoid cystitis.

Central degeneration of von Brunn nests leads to cyst formation and is termed cystitis cystica. Von Brunn nests, cystitis cystica, cystitis glandularis, and colonic metaplasia form a continuum of metaplastic lesions in the urothelium. Microscopically, cystitis cystica and cystitis glandularis are common lesions, approaching a frequency of 60% in autopsy bladders. They usually have central eosinophilic proteinaceous fluid, and when the central lumen of a nest exceeds several millimeters, the remaining urothelial cells in the periphery become flattened and attenuated. In most cases of cystitis cystica, the luminal row of cells have an abundance of eosinophilic cytoplasm and a cuboidal or columnar shape. A diagnosis of cystitis glandularis is reserved for those nests in which there is colonic type metaplasia with goblet cells identical to those of the large bowel [7]. In this study, one case showed features of cystitis cystica.

Bladder diverticula are relatively common and frequently without clinical significance. However, progressive enlargement rarely leads to stagnation of urine in them. This stagnation predisposes the bladder to calculus formation and infection. Bladder diverticula occur in patients of all ages, with most cases occurring in men older than 50 years, secondary to prostatic hyperplasia [8]. In our study, we had one case of diverticultitis in a 60 year old man with nodular prostatic hyperplasia. He also showed grade 1 renal parenchymal changes.

To conclude, in symptomatic lower urinary tract disease, cystoscopy and histopathological evaluation is rewarding in the diagnosis of various non-neoplastic causative lesions. Awareness of these entities facilitates easy diagnosis and differentiation from malignant processes.

References

1. Harik LR, O'Toole KM. Nonneoplastic Lesions of the Prostate and Bladder. Arch Pathol Lab Med 2012;136:721-34.
2. Hill GS. Cystitis. In: Uropathology. 1st ed. New York: Churchill Livingstone 1989, 431-50.
3. Shrestha EP, Karmacharya K. Profiles of histopathological lesions of urinary bladder: A five years study. Journal of Pathology of Nepal 2016;6:1001-4.
4. Susmitha S, Patil GS, Patil SB. A Study on Histopathological Spectrum of Lesions in Urinary Bladder Specimen. Annals of Pathology and Laboratory Medicine 2018;5(5):491-4.
5. Goyal VK, Vyas SP, Kothari DC. Spectrum of Lesions in Urinary Bladder Biopsies: Histopathological Study. Int J Dent Med Res 2015;1(6):42-6.
6. Mandal AK. Follicular cystitis – a case report. Indian J Pathol Microbiol 1999;42(4):503-4.
7. Petersen RO, Sesterhenn IA, Davis CJ. Urinary bladder. In: Urologic pathology. 3rd ed. Philadelphia: Lippincott Williams and Wilkins 2009, 175-207.
8. Young RH. Non-neoplastic disorders of the urinary bladder. In: Bostwick DG, Cheng L, editors. Urologic surgical pathology. 2nd edition. St. Louis: Mosby 2008, 220-237.
9. Sarma KP. On the nature of cystitis follicularis. J Urol 1970;104:709.
10. Hill GS. Cystitis. In: Uropathology. 1st ed. New York: Churchill Livingstone 1989, 431-50.
11. Epstein JI, Amin MB, Reuter VE. Biopsy interpretation series. Biopsy interpretation of the bladder. 2nd edition. Philadelphia: Lippincott Williams and Wilkins 2010, 226-59.
12. Verhagen PCMS, Nikkels PGJ, Jong TPVM. Eosinophilic cystitis. Arch Dis Child 2001;84:344-6.