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Non-neoplastic urothelial lesions and mimickers of malignancy: Take Cognizance - Avoid negligence

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Abstract
Background: The differential diagnosis of urothelial neoplasms also includes several histologic mimics, the importance of which cannot be overemphasized since misdiagnosis could have serious clinical and prognostic implications.
Aims: To study the variety of non-neoplastic lesions of the urothelial tract that could potentially be confused with urothelial neoplasms.
Material and Methods: A retrospective and prospective study of five years duration was done at a tertiary care hospital including 55 cases of non-neoplastic urothelial lesions. Results were analysed using SPSS22.
Results: Out of 43.62% of cases clinically suspicious for malignancy, majority (18.18%) were florid Proliferation of von brunn nests. Out of 56.3% cases clinically non-suspicious for malignancy majority were nonspecific cystitis (12.72%). The nonneoplastic lesions were more common in males (83.3%). The mean age was 45.6 yrs.
Conclusions: Diagnostic awareness of salient histomorphologic features of the benign mimickers of urothelial neoplasms is critical to avoid rendering false positive diagnoses of malignancy.

Keywords: Florid proliferation of von brunn nest, follicular cystitis, interstitial cystitis, nephrogenic adenoma.

Introduction
A plethora of lesions encompassing inflammatory, proliferative epithelial lesions and metaplastic phenomena are seen in the urothelium presenting with nonspecific signs and symptoms. Most of these lesions have been well described and the more common ones readily recognized [1]. Although they are distinctive, the uncommon lesions may pose a diagnostic challenge because of lack of familiarity with the lesion as in case of Nephrogenic adenoma and presentation as an intravesical mass as in Florid proliferation of von Brunn nests [2]. Their morphologic features closely mimic those of a neoplasm, making interpretation difficult. Bladder lesions are evaluated by limited sampling methods like cystoscopic biopsies and transurethral resection procedures, providing a small sample size coupled with cautery artefact thus raising the potential for diagnostic errors adversely affecting subsequent clinical management [3].
The lesions discussed herein include a spectrum of epithelial proliferative changes that the bladder mucosa may exhibit - inflammatory lesions and metaplastic processes with emphasis on the diagnostic pitfalls associated with these lesions and the role of ancillary techniques to distinguish the invasive carcinomas from their mimickers. It is crucial for the Pathologist to recognise these mimickers so as to avoid over diagnosis and for the Urologists to avoid inappropriate aggressive therapy.

Materials and methods
A retrospective and prospective study of five years duration from December 2014 to December 2019 was done in a tertiary care hospital. The study included all the non-neoplastic lesions as well as clinically suspected cases of malignancies of the bladder, urethra, renal pelvis and ureter which were histopathologically proven to be nonneoplastic. A total of 55 cases were included in the present study. The details of the patient, clinical history and cystoscopic findings were retrieved and reviewed by the authors. The clinical records

were reviewed wherever available. Data was analysed using SPSS 22. The results were expressed as mean for quantitative variables and as percentages for qualitative variables.

Results

The spectrum of non-neoplastic lesions encountered in the study are shown in Table 1. In 43.62% (24/55) of the cases the urologists expressed clinical suspicion of neoplasm due to the cystoscopic appearance of papillary lesions/bulbous growth. The relevant cystoscopic and radiological findings in clinically suspicious cases wherever available are mentioned in Table 2.

Table 1: Non neoplastic lesions of urothelial tract

NNL	Clinically suspicious of malignancy		Not suspicious of malignancy	
	No. of cases	%	No. of cases	%
FPVBN with CC & CG	10	18.18%		
CG	5	9%		
CC	5	9.%		
Nephrogenic adenoma	1	1.81%		
Urethral caruncle	3	5.45%	4	7.27%
Sub-acute cystitis			1	1.81%
Follicular cystitis			4	7.27%
Eosinophilic cystitis			4	7.27%
Interstitial cystitis			4	7.27%
Squamous metaplasia			4	7.27%
Non-specific cystitis			7	12.72%
TB cystitis			2	3.63%
Granulomatous cystitis			1	1.81%
Total no. of cases: 55	24	43.62%	31	56.3%
FVBN: Florid proliferation of von brunn nest, CG: Cystits glandularis, CC: Cystits cystica, TB cystitis: Tuberculous cystitis				

Table 2: Cystoscopic and radiologic findings in clinically suspicious cases

	Lesions	Age	Sex	Clinical feature	Site	Cystoscopic finding	Radiologic finding
1	FVBN with CC and CG	40	M	LUTS	B	Thickened bladder wall with plenty of trabeculations. Ureteric orifices couldn't be visualised.	CECT-Broad based tumour at the base of bladder /trigone
2	FVBN, CC & CG with intestinal metaplasia	33	M	Hematuria, frequency of micturition	B	Papillary lesion in the bladder wall, trigone, ureteric orifices	USG- Lesions noted in the trigone/ bladder wall ?growth
3	Subacute cystitis	75	M	LUTS	B	Papillary projection with calcification over the wall of bladder	USG-Bladder wall thickening
4	CG	32	M	LUTS	B	Bulbous areas at trigone	USG – normal
5	Urethral caruncle		F	Obstructive LUTS	Uth	1.5X1cms dark red mass found on the post. Lip of external meatus while inserting 14- Fr. Urethral catheter. Cystoscopy was normal	USG- normal
6	FVBN, CC CG	35	M	LUTS	B	Multiple edematous papillary frond in the bladder trigone involving uretreric orifice, B/l lateral wall	USG- Frond like projection in the base of urinary bladder involving vescicoureteric junction with mild prominence of distal ureter bilateral s/o CC
7	Nephrogenic Adenoma	6	M	Left flank pain	UO	Nodular thickening at site of reimplantation	USG: Left kidney shows hydronephrosis.
8	FVBN, CC	71	M	Recurrent UTI	U	Polypoidal lesion in bladder	USG - ? focal bladder wall thickening
9	FVBN	62	M	Haematuria	B	Nodular Mass	USG: Irregular thickening in anterior bladder wall.?neoplastic
10	FVGN with CG	42	M	Dysuria	B	Polypoidal lesion in urinary bladder wall and at vesicoureteric junction	USG- Suspicious thickening at uv junction
11	Chr. NSC	30	F	Dysuria	B	Nodular lesions at trigone	USG: normal
12	CG	65	M	Recurrent UTI	B	Focal erythematous areas in bladder	USG: normal
FVBN: Florid proliferation of von brunn nest, CG: Cystits glandularis, CC: Cystits cystica, Chr. NSC: Chronic non-specific cystits B: Bladder, U: Ureter, Uth: Urethra, UO: Ureteric orifice							

Most of the patients presented with lower urinary tract symptoms (LUTS) of varying severity. All patients were treated based on their clinical presentation in correlation with the histopathological findings. The patient with nephrogenic adenoma had vesicoureteric reflux for which ureteric reimplantation had been done earlier. In keeping with the diversity of lesions the study also demonstrated a diverse age group ranging from 6 to 73yrs. Youngest patient in the present study was six years with nephrogenic adenoma and oldest was 73 yrs with non-specific cystitis. The mean age was 45.6 yrs. The most common site of nonneoplastic lesions was in the bladder 83.63% (46/55),

followed by urethra 12.7% (7/55 cases) and a single case involving the ureteric orifice 1/55 (1.81%) and ureter 1/55 (1.81%). Florid von brunn nests were the most common lesions amounting to 18.18% cases (10/55) in the present study.

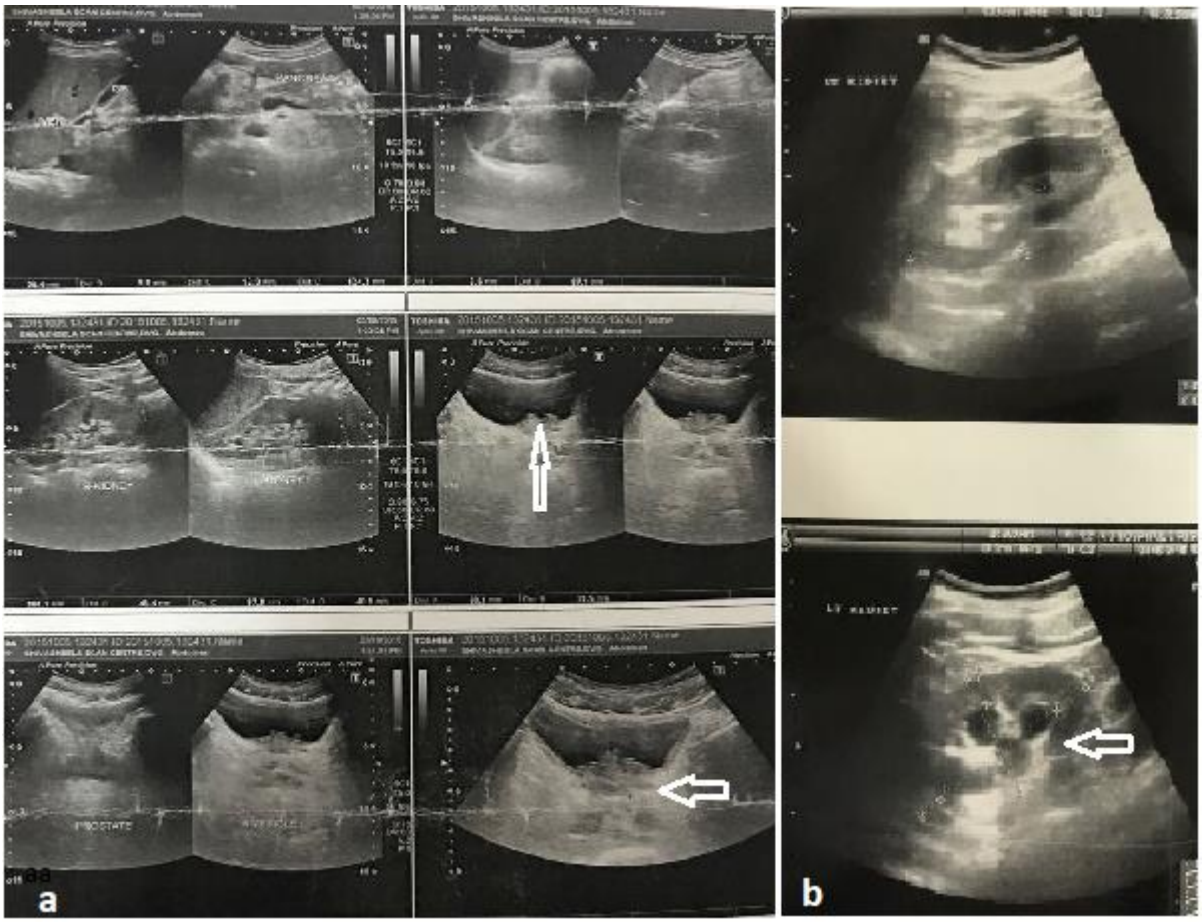

Fig 1: (a) shows CT of Florid proliferation of Von brunn nest mimicking malignancy radiologically. (b) Shows radiograph of nephrogenic adenoma showing left kidney with hydronephrosis

Discussion

We present a concise review of a variety of non-neoplastic lesions and metaplastic phenomena seen in the urothelial tract with a few mimicking urothelial malignancies clinically, cystoscopically and histologically especially in the bladder.

Out of 55 cases of non-neoplastic lesions of the bladder, 24 cases (43.7%) were clinically suspicious of malignancy and the lesions included five entities, 18.18% cases of florid proliferation of von brunn nest, 9.09% cases each of cystitis cystica & cystitis glandularis, 1.81 % case of nephrogenic adenoma and 5.45% cases of urethral caruncles. All these cases posed diagnostic challenges either clinically/histologically or both.

The cystoscopy and radiologic features of clinically suspicious cases wherever available are mentioned in table 2. Histological features were quite challenging in few of these cases. One case of Florid proliferation of von brunn nests presenting as a mass clinically, mimicked nested variant of urothelial carcinoma on cystoscopic biopsy displaying extensive proliferation of large nests of urothelial cells (Figure 2a, 2b). However, cystectomy specimen did not show any features of invasion into the muscularis propria and the nests were parallel to the surface epithelium extending to the same horizontal level at the base of the proliferation. There was absence of cytologic atypia. All these features favoured the diagnosis of a florid proliferation of von brunn nests over nested variant of urothelial carcinoma. This unintended misdiagnosis turned detrimental to the patient as the patient expired following cystectomy due to septicaemia.

Deepti *et al*. reported Florid proliferation of von brunn nests [FVBN] as the most treacherous entity which can be mistaken for malignancy especially on a superficial biopsy. It is rare, with a reported prevalence of 0.3% [4].

Brunn nests represent invaginations from the surface urothelium that form aggregates of urothelial cells. These nests may occasionally lose their connection to the surface and become isolated in the lamina propria and may resemble the nested variant of invasive urothelial carcinoma [NVUC] [2] as seen in one of the cases in the present study. In fact, in some cases, it is very difficult to establish an unequivocal diagnosis of NVUC in the biopsy material until multiple biopsies are performed [4].

FVBN represents a true diagnostic challenge, cognizance of this entity will help the pathologist to avoid an erroneous diagnosis of malignancy in this non-neoplastic lesion.

One of the lesions in the ureter showed hyperplastic nests of von brunn extending into the muscular layer making it even more difficult to render a diagnosis of a nonneoplastic lesion for this entity.

A study by Volmar *et al.* [2] on morphologic and

immunohistochemical comparison of Florid von Brunn nests to the nested variant of urothelial carcinoma showed wide variation in staining for MIB-1, p53, p27, and cytokeratin 20, such that except for a few cases, a specific cut-off value could not be determined for diagnostic purposes. These IHC features underscore the importance of morphologic assessment in the distinction of florid von Brunn nests and NVUC. However other studies showed that NVUC consistently showed higher MIB-1 labelling compared with benign proliferating lesions, such as von Brunn nests, cystitis cystica, and inverted papilloma. Therefore the role of IHC remains inconclusive [2].

Cystitis Cystica and Cystitis Glandularis comprises of 9.09% cases each in the present study. It represent a continuum of proliferative and presumed reactive changes that can involve von brunn nests anywhere along the urinary tract and are usually named accordingly (cystitis cystica, ureteritis cystica, urethritis cystica) [5]. It is characterized by proliferation of von brunn nests with central cystic luminal spaces that often contain eosinophilic secretions [6]. (Figure 2 c, d). It is due to a local immune response to a chronic inflammatory stimulus and has been associated with recurrent urinary tract infection. 90% of our patients with cystits cystica also presented with recurrent UTI similar to study done by Bastianpillai C [6].

Cystitis glandularis is characterised by cystic spaces lined by cuboidal/ columnar epithelium; if that epithelium acquires intestinal-type goblet cells, then the term cystitis glandularis with intestinal metaplasia is used. (Figure 2e, 2f) One of the cases showed nests of epithelial cells with extravasated mucin. When associated with extravasated mucin [6] in the stroma the latter can be misdiagnosed as invasive adenocarcinoma.

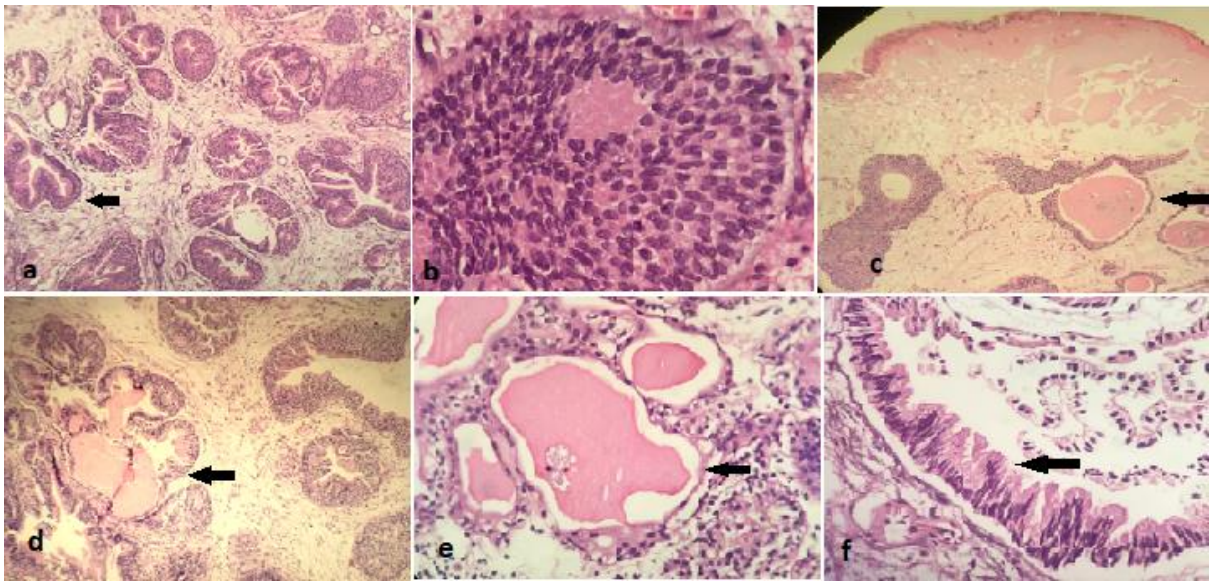

Fig 2: (a, b): Photomicrograph of Florid proliferation of Von brunn nests (200X) show large nests of urothelial cells (H &E, 400X, arrow) mimicking nested variant of urothelial carcinoma. Note the regular distribution of the nest and absence of cytologic atypia. Figure 2 (c, d, H &E, 200X arrow) Cystitis cystica is characterized by variably sized nests of urothelial cells with central cystic luminal spaces that often contain eosinophilic secretions. Figure 2 (e, f, H &E 400X) Cystitis Glandularis showing glandular metaplasia (f, arrow) in the epithelium lining the cysts.

Cases of cystitis glandularis co-existing with urothelial carcinomas were excluded in the present study. However, the differential diagnosis of these lesions includes invasive urothelial carcinoma with glandular differentiation, the microcystic variant, and the tubular variant. The presence of epithelial structures in an orderly fashion just beneath the urothelium with absence of significant cytologic atypia and desmoplasia should steer one away from a diagnosis of invasive adenocarcinoma [5]. NVUC are often also confused with cystitis cystica, cystitis glandularis, nephrogenic metaplasia but can be differentiated by the presence of poorly defined and confluent nests of relatively bland neoplastic cells that infiltrate deeply into the wall and often associated with an inflammatory or desmoplastic response [7].

Cystitis glandularis can co-exist with bladder carcinoma, however its nature with regard to premalignant risk especially in CG displaying extensive proliferation is the subject of much debate due to lack of definitive evidence [6, 8].

Nephrogenic adenoma of the urinary bladder (NAUB) which could inadvertently be misdiagnosed is a rare lesion seen over a wide age range (4–81 years). 10% of NAs have been observed in children [9]. Fili RA *et al*. reported ureteric reimplantation as the most important predisposing factor in a pediatric population as was seen in our case [10] In the present case patient presented with a polypoid mass at the ureteric orifice mimicking carcinoma grossly and suggesting adenocarcinoma microscopically. But with relevant history of ureteric reimplantation for vescicoureteric reflux, age of the pateint and knowledge of different growth pattern, cytologic features and characteristic stroma of NA it was possible to avoid misdiagnosis. Differentials to be kept in mind in older patients with the above microscopy are adenocarcinoma/invasive urothelial carcinoma with glandular differentiation/microcystic variant, signet cell and clear cell carcinoma, metastatic prostatic/ renal cell carcinoma in [11].

Nephrogenic adenoma is commonly seen in the urinary bladder (80%); however, urethra (12%) and ureter (8%) can

also be involved [12].

Grossly NA's appear papillary (56%), polypoid, (10%), fungating or sessile (10%). On cystoscopy, the sessile lesions appear friable & velvety, mimicking urothelial carcinoma in situ. Most NAs (62%) are small lesions (1 cm), rarely they are as large as 7 cm [12, 13].

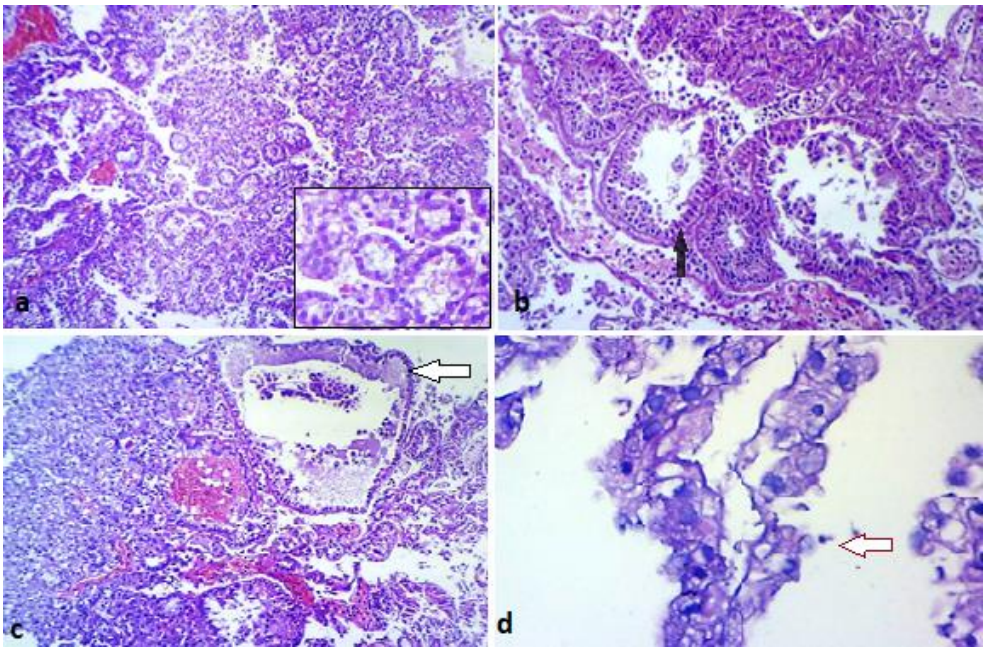

Fig 3: (a, b H&E, 200X) Photomicrograph of nephrogenic metaplasia showing haphazardly arranged tubules predominantly with an occasional back-to-back architecture in the lamina propria, lined by cuboidal to low columnar cells (inset) with hobnailing (arrow). The cytoplasm is pink and occasionally clear. Figure 3(c), H & E 200X (arrow) shows the second pattern displaying cysts and cystic dilatation of the tubules accompanied by eosinophilic secretions. Fig 3(d), H & E 400X (arrow) the third pattern shows a polypoid to papillary architecture usually lined by a single layer of cuboidal to low columnar cells with clear cytoplasm

Histologically, the most common pattern is the tubular architecture. (Figure 3 a, b). The tubules are simple and separate, with an occasional back-to-back architecture. Mitoses, when present are rare. The stroma lacks the desmoplastic response. A small percentage show a prominent basement membrane material surrounding the tubules. The second pattern includes cysts and cystic dilatation of the tubules (Fig 3c), accompanied by eosinophilic or basophilic secretions. The third pattern shows a polypoid to papillary architecture (Fig 3d).

The cells lining the tubules, cysts and papillae are lined by a single layer of cuboidal to low columnar cells with scant pale cytoplasm and are occasionally clear [7]. This entity comprised 1.81% cases in the present study and demonstrated all three patterns. Figure 1(b) shows radiograph of nephrogenic adenoma.

A study by Oviedo SP *et al*. described the presence of a flat pattern of NA associated with other traditional patterns (tubular, polypoid, papillary) which was first suspicious for flat urothelial atypia on H&E sections but later was confirmed by PAX2 and PAX 8 IHC as flat NA [11].

Nephrogenic adenomas especially focal solid/ tubular pattern rarely involves the deep lamina propria or superficial muscular propria thus mimicking certain urothelial carcinomas with deceptively bland features, such as the NVUC, prostatic adenocarcinoma and clear cell adenocarcinoma and pose diagnostic difficulty [9].

Immunohistochemistry, especially p63 and PAX2, may be useful in resolving this diagnostic conundrum as urothelial carcinomas with deceptively bland features (nested and/or urothelial carcinoma with small tubules) are strongly positive for CK7, p63, and 34bE12, while nephrogenic adenoma is positive with AMACR, PAX2, and CK7, variably positive with 34bE12, and negative with p63. Although NA are considered to be benign lesions, malignant transformation has been reported suggesting premalignant potential [14].

Another rare entity that may mimic NA is clear cell adenocarcinoma which shows a strong female predilection. They are more common in the urethra than the urinary bladder and show similar patterns as seen in NA but are infiltrative, high grade, with frequent mitoses, obvious nuclear atypia and pleomorphism, necrosis, prominent areas of solid growth, and extensive muscle invasions, features which are absent in NA. Immunohistochemistry has limited utility in distinguishing NA-like clear cell adenocarcinoma from NA. PAX2 expression appears to be more useful, as it was more frequent in NA (89%) than clear cell adenocarcinoma (29%–32%) [15].

Another nonneoplastic lesion of the lower urinary tract is urethral caruncle. These are polypoidal inflammatory lesions commonly seen in elderly women and have to be distinguished from inflammatory pseudotumor, urothelial carcinoma or metastatic tumour, as most of the urethral carcinomas present in a similar fashion. Histologically caruncles resemble hemangiomas with intense acute and chronic inflammatory infiltrate. The overlying urothelium may be hyperplastic, ulcerated and exhibit squamous or glandular metaplasia. In the present study, 7.27% of cases were clinically not suspicious of malignancy and only 5.45% case was suspicious of malignancy clinically. Most of them presented with dysuria/hematuria [13].

Inflammatory lesions

Cystitis can occur due to both infectious aetiologies including bacterial, viral, and rarely fungal, as well as non-infectious origins- follicular cystitis, interstitial cystitis, eosinophilic cystitis and drug-induced cystitis [3, 16]. Prominent inflammation frequently associated with Invasive urothelial carcinoma in conjunction with tissue damage and repair seen in TUR procedures can sometimes obscure the neoplastic cells. These appearances can also be mimicked by lesions associated with a prominent inflammatory infiltrate, such as follicular and eosinophilic cystitis. Therefore, careful histologic evaluation should be able to resolve most of these diagnostic challenges [17].

Among the non-infectious cystitis, Interstitial Cystitis(IC) is a syndrome characterized by bladder pain and irritative bladder symptoms for more than 6 months duration and has a female predilection. It is often a diagnosis of exclusion. A noxious stimulus persisting for a longer duration initiates a cascade of events, resulting in a vicious cycle of persistent inflammation and recurrent injury to bladder epithelium. Although these changes are likely to contribute to pain and urinary symptoms, precise mechanisms are unclear [18]. 7.27% cases in the present study showed interstitial cystitis with 98% of case presenting with LUTS.

In a study by Kullmann FA on interstitial cystitis, the cystoscopy revealed petechial haemorrhages (glomerulations), ulcers (Hunner's ulcers), denudation, tears and thinning in cases of interstitial cystitis [19, 20]. Cystoscopically all cases (100%) in the present study showed peticheal haemorrhages. A cystoscopic biopsy is performed primarily to rule out other possible confounding etiologies such as carcinoma in situ. In the present study the histologic findings s showed edema and congestion of the lamina propria with mononuclear inflammatory infiltrate and a few cases exhibiting ulceration/denuded mucosa. (Figure 4b).

Another non-infectious condition - Eosinophilic cystitis (EC) is a rare disease described by Brown and Palubinskas in 1960 [21]. Seen commonly in adults, affecting men and women equally. In children there is a slight male predominance. Eosinophilic cystitis has been associated in patients with allergies and atopy, however the aetiology is unknown [22].

The manifestations of EC vary within a large spectrum from mild irritative bladder symptoms to a large bladder mass simulating infiltrative cancer with upper tract obstruction. Cystoscopically it is difficult to distinguish eosinophilic cystitis from other forms of cystitis or bladder malignancy. A raised velvety, polypoid, oedematous lesion, suspicious for carcinoma with ulceration and necrosis is sometimes seen in which case biopsy would be mandatory to confirm the diagnosis of eosinophilic cystitis [21].

The present study showed 7.27% of the cases of eosinophilic cystitis presenting with lower urinary tract symptoms [LUTS] and one case with vescicovaginal fistula. Microscopically the lesion is characterized by the presence of a dense inflammatory infiltrate composed primarily of eosinophils involving the bladder wall (Figure 4c). The eosinophilia can be accompanied by muscle necrosis and edema [3].

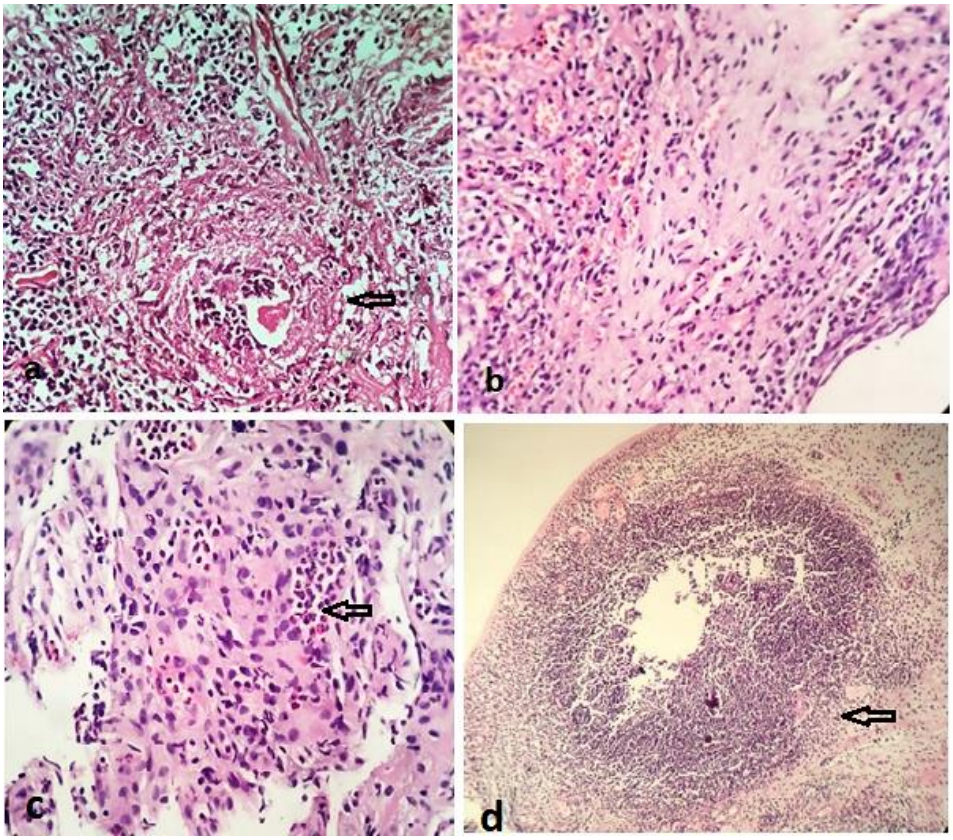

Fig 4: (a): Photomicrograph of tuberculous cystitis shows confluent granulomas (arrow) with occasional langhans giant cells and caseating necrosis H &E, 200X. 4(b) Photomicrograph of Interstitial cystitis show congested and oedematous lamina propria with dense nonspecific inflammatory infiltrate and patchy fibrosis H &E 200X. 4(c) Photomicrograph of Eosinophilic cystitis show aggregates of eosinophils, sheets of lymphocytes and plasma cells H &E 200X (arrow). 4(d) Photomicrograph of Follicular cystitis show numerous lymphocytes and plasma cells admixed with lymphoid follicles (arrow) in the bladder mucosa and submucosa. H &E (200X).

Follicular cystitis (FC) is a rare nonspecific inflammatory disease of the bladder which primarily affects women [23]. This can have a variable presentation but most typically presents similarly to other chronic cystitis with dysuria and increased urinary frequency [24]. In the present study follicular cystitis accounted to 7.27% of the cases, all the cases were seen in females and all cases presented with LUTS. Cystoscopic examination revealed white nodules most commonly in the area of the trigone in 80% cases, often on a background of erythematous mucosa. On Gross pathological examination the lesions may appear granular and solid, nodular, erythematous or edematous. Histologically, numerous plasmacytic cells and lymphocytes with lymphoid follicles scattered within the bladder mucosa and submucosa were seen (figure 4d). Sometimes the overlying urothelium may display mild atypia or metaplasia. In the present study we did not face any diagnostic difficulty for this entity.

The pathologic differential diagnosis includes malignancies such as follicular lymphoma and other Non-Hodgkin's lymphomas. The primary urinary tract lymphomas are extremely rare and among them low grade MALT Lymphomas are the most frequent in the bladder [24]. In the absence of specific diagnostic modalities, cystoscopy followed by histopathological examination is the accurate method to 16 eliminate clinical suspicion.

Tuberculous cystitis accounts for 3.63% of the cases which are not suspicious for malignancy in the present study. The Genitourinary tract is the most common site of extra-pulmonary TB and spread occurs through hematogenous route. The most common site of GUTB is the kidney with the bladder being secondarily involved either by ascending or descending infection [25]. A wide spectrum of pathological changes are seen in genitourinary tuberculosis varying from normal morphology to extensive scarring of the kidney, bladder, and epididymis with auto cystectomy [26].

The bladder changes in early stage are usually nonspecific and gives rise to irritative voiding symptoms. Chronic inflammation and fibrosis lead to reduced compliance which manifests as increased frequency of micturition while extensive bladder involvement, mural fibrosis and contracture results in 'Thimble bladder' which may manifest with urinary incontinence. Similar process at the vesicoureteric junction gives rise to 'golf hole ureter' appearance. This was also noted in the present case. The diagnosis of Tuberculous cystitis is made by the demonstration of mycobacterium in the urine or body fluid, histopathological and radiological examination. Newer examinations such as radiometric liquid culture systems (ie, BACTEC, Becton Dickinson, USA) and Polymerase chain reactions give rapid results and are highly sensitive in the identification of mycobacterium [27]. Histopathology in the present case revealed multiple confluent granulomas with occasional Langhans giant cells and caseating necrosis. (Figure 4a). AFB stain was positive in this case.

Squamous metaplasia is typically seen as white or grey-white patch on cystoscopy. Microscopic examination reveals stratified squamous epithelium with or without keratinization that is cytologically bland with orderly maturation [1]. Keratinizing squamous metaplasia (KSM) is considered a preneoplastic lesion [28]. 7.27% of the cases in the present study showed squamous metaplasia. Long-term catheterization, urinary lithiasis, chronic urinary tract obstruction, urinary fistulae, bladder exstrophy, neurogenic bladder, previous bladder surgery, pelvic radiotherapy, parasitic colonization, and vitamin A deficiency are also associated with this disease [29]. Any degree of atypia should be viewed with suspicion because it may indicate the presence of squamous cell carcinoma in adjacent unsampled mucosa or elsewhere in the specimen [1].

Conclusion

Non-neoplastic lesions of the urothelial tract encompass a wide variety of reactive changes that can occur in the urothelium, as well as hyperplastic lesions or reactive proliferations that could be misdiagnosed as malignant. In our increasingly litigious society these errors could prove to be our undoing. Cognizance of these diagnostic conundrums occurring in the renal pelvis, ureter, bladder and urethra, with knowledge of their salient features, preneoplastic potential, and relevant differentiating histological and immunohistochemical features will help pathologists confidently diagnose malignancy vis-a-vis its benign mimickers and guide the urologists in choosing appropriate therapy as well as follow-up for their patients.

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