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Uncommon Tumors of Urinary Bladder

Madhumita Mukhopadhyay[1]*, Binata Bandopadhyay[2], Subhamoy Saha[3], Biswanath Mukhopadhyay[4]

[1]Former Professor, Department of Pathology IPGMER, Kolkata, HOD Pathology JISMSR, West Bengal, India
[2]Senior Resident, Department of Pathology, Murshidabd Medical College, Murshidabad, West Bengal, India
[3]PGT, Department of Pathology, IPGMER, Kolkata, West Bengal, India
[4]Senior Consultant, Department of Pediatric Surgery, Apollo Multispeciality Hospital, Kolkata, India

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***Corresponding Author**
Madhumita Mukhopadhyay

Former Professor, Department of Pathology,IPGMER, Kolkata, HOD Pathology JISMSR, West Bengal, India

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A B S T R A C T

***Introduction*:** Urinary bladder cancer is a prevailing cancer of the urinary system. Worldwide it is the ninth most common type of cancer. There are broadly two histological types of bladder cancers: urothelial and non- urothelial. Urothelial carcinoma is the predominant type with an incidence of 90-95%. Non-urothelial cancers are further subdivided into epithelial and nonepithelial. Epithelial cancers include squamous cell carcinoma, adenocarcinoma,andsmall cell tumors whereas nonepithelial cancers which are further more rare, include sarcomas, melanomas, lymphomas,and paragangliomas. Neurofibromas of thegenitourinary tract arise, from nerves of thepelvic, vesical and prostatic plexuses. Cystitis glandularis is also a very rare benign proliferative disease of urinary bladder mucosa and is usually a microscopic diagnosis and rarely manifests as a large visible macroscopic mass of urinary bladder.

***Materials and Methods*:** This is a prospective study conducted in a tertiary care hospital comprising six cases of unusual urinary bladder lesions. We studied the cases according to their age, sex, clinical presentation, location within the bladder, radiological findings, histopathological findings, immunohistochemical findings and treatment provided.

Results: This study comprisessix cases of unusual primary urinary bladder lesions which includes one case of squamous cell carcinoma, mucinous adenocarcinoma, clear cell carcinoma, paraganglioma, neurofibroma cystitis glandularis each. The patients belong to a wide age range between 3rd to 7th decade. There is male predominance. Hematuria is the common clinical presentation in all of them. Different locations within the bladder is involved in all these six cases. Histopathological examination followed by immunohistochemical staining of the formalin fixed paraffin embedded tissue sections confirmed their diagnosis.

***Conclusion*:**There are several histological variants of urinary bladder cancers, however squamous cell carcinoma, mucinous adenocarcinoma, and clear cell carcinoma are extremely rare. Extensive work-up, including immunohistochemical studies are required to rule out both the possibility of other sites of these primary tumors and possibility of metastasis. Isolated urinary bladder neurofibromas are extremely rare which requires clinical follow up to monitor potential recurrence or progression. Paraganglioma are even more rare and incidentally detected. Cystitis glandularis is a chronic disease and should be considered as a distinct clinical entity.

Keywords: Clear cell carcinoma, Cystitis glandularis, histopathological examination, immunohistochemistry, mucinous adenocarcinoma, Neurofibroma, paraganglioma, Squamous cell carcinoma, Transurethral resection of bladder tumor.

INTRODUCTION

Urinary bladder (UB) cancer is a prevailing cancer of the urinary system, and worldwide it is the ninth most common type of cancer. There are broadly two histological types of bladder cancer: urothelial and non urothelial. Urothelial carcinoma is the predominant type comprising 90-95% of bladder cancers. Non urothelial cancers are further

subdivided as epithelial and nonepithelial. Squamous cell carcinoma (SCC), adenocarcinoma, small cell tumors are of epithelial origin [1], whereas nonepithelial cancers which are further more rare includes sarcomas, melanomas, lymphomas, paragangliomas. SCC of UB comprises 2% to 5% of all bladder cancers in western countries, while less common in comparison to urothelial carcinomas, it is the second most common histological subtype [2]. The leading cause of SCC of UB in regions without schistosoma infection is chronic irritation, often found to be associated with prolonged indwelling catheters seen in patients with spinal cord injuries [3]. In patients where SCC of UB is not associated with schistosomiasis, the diagnosis occurs at alate stage and presentswitha poor prognosis [4]. Adenocarcinoma of UB represents 0.5% to 2% of all malignant tumors, with mucinous subtype being extremely rare [5]. Primary bladder adenocarcinoma (PBA) has overlapping histological and immunohistochemical features with adenocarcinomas emerging from other primary sites like colorectal and gynaecological malignancies [6]. Hematuria is the most common clinical presentation in more than 90% of the patients and surgery is the best approach for its treatment [7]. Clear cell carcinoma (CCC) of UB is a morphological variant of adenocarcinoma of UB which mimics the mullerian type of CCC of thefemale genital tract [8]. Due to the rarity of primary bladder CCC, less is known about the biology of this disease entity. Paraganglioma of UB are tumors of chromaffin tissue which originates from the sympathetic innervations of UB. It is a very rare tumor thatconstitutes less than 1% of all paragangliomas and less than 0.05% of bladder tumors [9]. Often incidentally detected. Only 1% to 3% secretes enough catecholamines to become clinically significant, but can develop unexplained hypertension, headaches, palpitations, hot flushes, sweating,and micturition syncope [9]. Neurofibromas (NFs) are generally associated with neurofibromatosis. However isolated cases of neurofibromas in UB are extremely rare and accounts for less than 0.1% of bladder tumors [10]. In the bladder, NFs originate in the nervous ganglia of the bladder wall and less than 70 cases have been reported [11]. Cystitis glandularis (CG) is a rare benign proliferative disease of UB mucosa, which is often encountered as an incidental finding and has a predilection for trigone of bladder. Risk factors include long standing inflammation from chronic irritation like indwelling catheters, infections,or stones [12].

MATERIALS AND METHODS

This is a prospective study conducted in a tertiary care hospital comprisingsix rare cases, involving the UB. Cases include SCC, mucinous adenocarcinoma, CCC, paraganglioma, NF, and CG, one case each, all were primary UB lesions. The majority of the patients were male and different locations within the bladder were involved by these lesions. Histopathological and immunohistochemical (in four out of six cases) analyses was performed on the formalin fixed paraffin embedded samples. The biomarkers tested in our tumor samples were CK 20, GATA3, CDX2, CK 7, p63, ER, PR. S100, synaptophysin and chromogranin. We studied the cases according to their age, sex, clinical presentation, location within the bladder, radiological findings, histopathological findings immunohistochemical findings and treatment provided. Informed consents were taken from all the patients.

RESULTS

CASE 1: Primary SCC of Urinary Bladder

A 70-year-old man presented to the out patient department (OPD) of surgery with a history of recurrent urinary tract infection (UTI) since last six months associated with sudden onset pain during micturition and hematuria since last one month. He was a known smoker since last 50 years. He was advised both routine and microscopic urine analysis, ultrasonography of the kidney ureter bladder (USG KUB) and other routine blood investigations. Urine analysis showed areddish hazy appearance and plenty of RBCs on microscopy. USG showed irregular thickened UB. Contrast enhanced computed tomography (CE-CT) of theabdomen-pelvis was then advised which showed a (26x37)mm isodense to hyperdense non pedunculated mass lesion with irregular margins involving the trigone of bladder without involving bilateral uretero-vesicular junction, suggestive of malignant UB neoplasm with wall invasion and involvement of iliac nodes. Patient underwent surgical procedure of transurethral resection of bladder tumor (TURBT) and was on chemotherapy. Gross examination showed multiple irregular white to grey coloured pieces of tumor mass, largest bit measuring 1.5cm x 0.5cm x 0.5cm. Microscopic examination showed tumor composed of neoplastic squamous cells arranged in sheets. Individual cells were large polygonal having moderately hyperchromatic to vesicular nuclei, prominent nucleoli, moderate amount of eosinophilic cytoplasm. Keratin pearls with individual cell keratinization was noted. (Fig 1) There was invasion of the muscle tissue by the tumor (Fig 2). There was no evidence of any urothelial components in this tumor, hence the diagnosis of pure SCC was given.

CASE 2: Primary Mucinous adenocarcinoma of Urinary Bladder

A 65-year-old-man presented with history of supra pubic pain for 6 months and intermittent hematuria for past 1 month. He was a non smoker and non drinker. He showed several investigation reports done in a private hospital among which CT scan KUB with contrast revealed a (28x35)mm polypoidal homogenous enhancing broad based space occupying lesion (SOL) from the roof of UB. He was again advised CE-CT of abdomen and pelvis which revealed asymmetric mural thickening in the UB wall in the postero-superior aspect (Fig 5). He underwent TURBT,and the specimen was sent to the department of pathology. We received multiple, irregular white to grey coloured pieces of tumor mass altogether measuring 20 cc. Histopathological examination (HPE) showed ill defined glands, nests of malignant

epithelial cells invading lamina propria and muscularis propria. There were abundant extracellular mucin with clusters of tumor cells floating in mucin lakes. The individual tumor cells show high nuclear-cytoplasmic ratio and moderate nuclear pleomorphism (Fig 3 & 4). Immunohistochemistry (IHC) showed CK 20 positivity (Fig 6) andCDX2 negativity.

GATA 3 negativity confirming primary mucinous adenocarcinoma of UB. The patient recovered well after surgery. He was recommended to undergo clinical and radiological follow up every year.

CASE 3: Primary CCC of Urinary bladder

A 60-year old female visited the OPD of Surgery department with chief complaints of recurrent UTI, episodes of urinary retention for 6 months associated with recurrent blood clots in the urine for last 3 months. There was no history of smoking or alcohol intake. CECT whole abdomen-pelvis revealed a large lobulated heterogeneously enhancing soft tissue mass over the base of bladder (Fig 7). Bilateral kidneys and ovaries were normal. She underwent TURBT and the specimen was received in our department as fragmented, greyish white soft tissue pieces altogether measuring 15cc. HPE revealed cuboidal to columnar cells arranged in nests, diffuse sheets invading the muscularis propria. Individual tumor cells showed mild to moderate nuclear atypia, abundant clear cytoplasm (Fig 8). There was absence of necrosis and mitotic activity was low. IHC was done which showed PAX 8 positivity, while the tumor was found negative for CK7, CK20, GATA3, p63, CDX2, ER, PR. Hence, from the radiological and IHC reports it was concluded that the tumor was not a metastasis from gastrointestinal tract, kidney and ovarian tumors, but a primary UB tumor.

CASE 4: Neurofibroma of Urinary Bladder

A 30-year-old male patient attended the surgery OPD with chief complaints of intermittent gross painless hematuria with amorphous clots for 6 months. Similar episode 2 years ago for which the patient was treated conservatively in the district hospital.The patient had gross hematuria 7 days before attending OPD. No history of fever or dysuria. The patient visited some local doctor and was advised to have aUSG whole abdomen. USG whole abdomen revealed thickened urinary bladder wall, one large hypoechoic solid mass in the lower part of UB measuring (9.8x10x8.3) cm (Fig 9). Then he was referred to our medical college. He was advisedto have aMRI pelvis which revealed 9.4cmx8cm intraluminal heterogeneous T_1-T_2 mass arising from postero-inferior and lateral wall of UB (Fig 10). He then underwent TURBT with fulguration of bleeding points, done under general anaesthesia. The TURBT specimen was then sent to the department of Pathology for HPE. Microscopy revealed a non encapsulated, moderately cellular, circumscribed lesion composed of spindle shaped cells with elongated, wavy nuclei loosely arranged in interlacing bundles and fascicles in a collagenous stroma (Fig 11). No necrosis or mitosis seen. The tumor cells were found to be positive for S100 protein by IHC (Fig 12). Hence, a final diagnosis of neurofibroma of UB was given. The patient denied any family history of Neurofibromatosis type 1 or other genetic syndromes in the family. However it was recommended that the patientshould undergo clinical and radiological follow up, but he was lost to follow up after 1 year.

CASE 5: Paraganglioma of Urinary Bladder

A 40-year-old female patient was referred to the surgery OPD following incidental detection of bladder lesion on pelvic USG for a complaint of per vaginal bleeding. She also complained of a sensation of incomplete bladder emptying. She was a known hypertensive and was on regulation medication. CT scan of abdomen and pelvis demonstrated a 25mm well circumscribed posterior bladder wall mass suspicious of bladder cancer. She underwent TURBT and the specimen was sent to the department of Pathology for HPE. Post operatively the patient was found to have normal blood pressure. Histological examination revealed round to polygonal cells arranged in nests or zellballen pattern surrounded by vascularized fibrous septa (Fig 13). Individual tumor cells have centrally located nuclei with salt and pepper chromatin and moderately abundant fine granular cytoplasm. The features were consistent with the diagnosis of paraganglioma, which was further confirmed by IHC. IHC revealed that the tumor cells were positive for synaptophysin (Fig 14) and chromogranin (Fig 15). Unfortunately there was no pre-operative and post-operative vanillylmadelic acid (VMA)/ catecholamine data, and the patient was lost to follow up.

CASE 6: Cystitis glandularis of Urinary Bladder

A 43-year-old man presented to the surgery OPD with chief complaints of urinary frequency, urgency and nocturia for the past 2 years, associated with intermittent gross hematuria for last 6 months There was no history of fever or burning sensation during micturition. Urine cytology revealed plenty of RBCs. CT scan KUB was suggestive of a well circumscribed fungating mass of size approximately 4.2cmx 3cm arising from the infero-posterior and right lateral surface of UB and extending to the bladder lumen (Fig.16). A complete TUR of the mass was performed followed by HPE, which revealed gland like lumens lined by columnar cells and surrounding chronic inflammatory cell infiltrate in the lamina propria. There was no evidence of Von Brunn nests, stromal reaction, significant atypia, or any evidence of malignancy. The histological findings were suggestive of cystitis glandularis. The patient recovered well post operatively and was on follow up for 1 year.

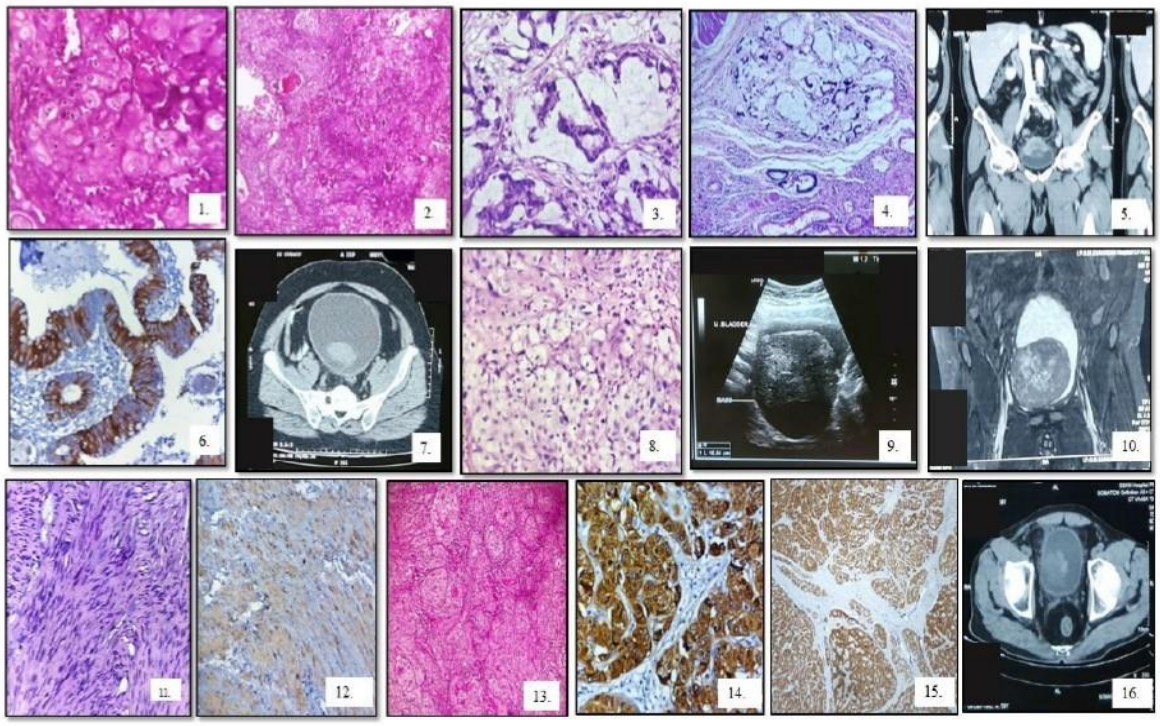

Fig. 1: H&E (400X) Sheets of large polygonal cells with moderately hyperchromatic to vesicular nuclei eosinophilic cytoplasm in Primary SCC of Urinary bladder.
Fig. 2: H&E (100X) Primary SCC with sheets of tumor cells invading the muscle layer of Urinary bladder.
Fig. 3: H&E (400X) Ill defined glands and nests of tumor cells floating in extracellular pool of mucin in Primary mucinous adenocarcinoma bladder.
Fig. 4: H&E (100X) Tumor cell nests in extracellular mucin pool infiltrating the lamina propria and muscularis propria of Urinary bladder in Primary mucinous adenocarcinoma bladder.
Fig. 5: CE-CT of abdomen and pelvis showing asymmetric mural thickening in the postero-superior aspect of bladder wall in Primary mucinous adenocarcinoma.
Fig. 6: IHC (400X) Positive expression of CK20 in the tumor cells in Primary mucinous adenocarcinoma bladder.
Fig. 7: CE-CT abdomen and pelvis showing a large lobulated heterogeneously enhancing soft tissue mass over the bladder base in Primary clear cell carcinoma
Fig. 8: H&E (400X) Nests of tumor cells with abundant clear cytoplasm in Primary clear cell carcinoma of Urinary bladder.
Fig. 9: USG whole abdomen showing thickened bladder wall and one large hypoechoic solid mass in the lower part of Urinary bladder in Neurofibroma bladder.
Fig. 10: MRI pelvis showing intraluminal heterogenous T_1-T_2 mass arising from postero-inferior and lateral wall of Urinary bladder in Neurofibroma bladder.
Fig. 11: H&E(400X) of Neurofibroma bladder showing spindle shaped cells with elongated wavy nuclei loosely arranged in fascicles in collagenous stroma.
Fig. 12: IHC (400X) Positive expression of S100 in the tumor cells in Neurofibroma of Urinary bladder.
Fig. 13: H&E (100X) Round to polygonal cells arranged in zellballen pattern in Paraganglioma of Urinary bladder in low power view.
Fig. 14: IHC (400X) Positive expression of Synaptophysin in the neoplastic cells in Paraganglioma of Urinary bladder.
Fig. 15: IHC (100X) Positive expression of Chromogranin in the neoplastic cells in Paraganglioma of Urinary bladder.
Fig. 16: CT scan KUB showing a circumscribed fungating mass arising from infero-posterior and right lateral surface of urinary bladder in Cystitis glandularis.

DISCUSSION

Primary SCC of UB is a relatively infrequent neoplasm [13]. Most SCC of the bladder are sessile, nodular, ulcerating and infiltrating. It is the most common malignant neoplasm in men with schistosomiasis [13], however, no such association was found in our case. SCC of UB is often associated with chronic bladder irritation which includes chronic or recurrent UTI, bladder calculi, indwelling urinary catheter, and long term exposure to cyclophosphamide [13]. The majority of the patients of SCC present with hematuria. The case we presented also had history of recurrent UTI and hematuria. For final diagnosis of pure SCC of UB,thorough sampling is required to exclude the presence of an invasive high grade urothelial carcinoma component, as done in our case; however,no evidence of urothelial carcinoma component was found in our case. Histological examination showed moderate grade SCC with muscle invasion in our case. Surgical resection is usually the treatment in case of localised disease, as this tumor may be resistant to chemotherapy and radiotherapy [13]. However,the case we discussed underwent TURBT and was on chemotherapy.

Primary mucinous adenocarcinoma of UB (PMAB) usually involves bladder dome, trigone and lateral wall, however in our case there was involvement of postero-superior aspect of bladder wall. It is crucial to distinguish PMAB from urachal carcinoma, as urachal carcinoma has a higher survival rate and better prognosis as compared to PMAB [14, 15]. Primary symptoms of PMAB arehematuria with or without signs of bladder irritation;in our case,there was presence of hematuria along with supra pubic pain. It is often difficult to differentiate PMAB from secondary involvement of bladder by adenocarcinoma arising from adjacent organs most commonly colorectum [14, 16].

Extensive workup including IHC staining, is essential to rule outthepossibility ofa primary tumor in the adjacent organs and the possibility of metastasis to confirm the diagnosis of primary bladder adenocarcinoma. IHC stains like CK20 is a marker of adenocarcinoma, CDX2 is a marker of colorectal malignancy, GATA3 is a marker of urothelial malignancy. In our case tumor cells were found to be positive for CK20, and negative for CDX2 and GATA3, confirming the diagnosis of PMAB, ruling out metastasis from colorectal adenocarcinoma [14, 16] and urothelial origin.

Primary CCC of UB is an aggressive disease, with muscle invasion found in half of the patients. It is more common in females, as seen in our case. It was suggested that the origin of CCC is from the mullerian duct, especially in patients with history of endometriosis. Though malignant transformation is not common in endometriosis, endometriosis can also occur in the non- gynaecological sites like UB which can lead to the development of CCC [17], however, no such association was established in our case. The current diagnosis of CCC of UB is based mainly on histologic and immunohistochemical staining characteristics. Currently there are no recommendations regarding the management of CCC of UB due to its rarity [17]. However, it was suggested that the treatment should largely follow the regular management of bladder cancer [18].

Isolated neurofibroma (NF) of UB is very rare and it arises from the nervous ganglia of the bladder wall. It commonly occurs in a younger age group and males are more commonly than females [11], as seen in our case. Clinical presentation of NF bladder includes hematuria, dysuria, irritative symptoms, in our case the patient presented with intermittent painless hematuria. Histological examination of NF shows diffuse proliferation of uniform medium sized spindle cells with elongated nuclei and S100 positive cytoplasmic processes. The histological features of NF simulates differential diagnosis of leiomyoma, low grade leiomyosarcoma, low grade malignant peripheral nerve sheath tumor, rhabdomyosarcoma. The distinctive clinical, histologic and immunohistochemical features usually help in definitive diagnosis [19, 20]. Though there are no follow up guidelines specific to NF of UB, it is recommended that the patient should undergo follow up which should include routine imaging to monitor local recurrence given the risk of malignant transformation. In a study of 10 year follow up of 4 cases of NF of UB,no malignant transformation was noted [19]. We also advised follow up post operative period. But the patient was lost to follow up after one year.

UB paraganglioma is not a common tumor and it was first described in 1953 by Zimmerman [21]. As per some previous studies, it is more common in middle aged females [19], as seen in our case. According to some other authors,there is no sex predilection for urinary bladder paraganglioma [9]. The most common presenting symptoms include painless gross hematuria, hypertension, and palpitation. However, in our case it was incidentally detected, and she did not have any complaints. But she was hypertensive. UB paragangliomas are extra-adrenal tumors, derived from neural crest and classically demonstrate groups of fairly uniform polygonal cells (zellballen pattern) [9]. Tumor cells were found to be positive for synaptophysin and chromogranin. As per some previous studies this tumor was found to be positive for synaptophysin, chromogranin, and CD56 [22]. Benign and malignant paragangliomas can not be differentiated morphologically and can be diagnosed after metastasis [23]. In our case there were no signs of metastasis. According to many experts, the standard treatment for paraganglioma is complete surgical removal, which includes partial or radical cystectomy. However, many surgeons still perform TURBT [22]. Life long follow up is necessary to detect recurrences [23].

TURBT has been done in our case andweadvised regular follow up for solitary, small tumors. The patient is doing well after one year.

Cystitis glandularis is a rare proliferative disorder which was first noted by Morgagni in 1761 [24]. It is commonly found on the trigone, neck of the bladder, lateral wall of bladder [24], There are two histological types of cystitis glandularis. Non-mucinous is the most common type and intestinal (mucinous) metaplasia type [25]. Clinical features are variable, it could remain asymptomatic or could present as irritative lower urinary tracthematuria. It is usually a microscopic diagnosis and overt UB mass is very rare [25]. Premalignant potential of cystitis glandularis is controversial. No evidence of carcinoma was noted in 1-17 years follow up of 166 patients of Cystitis glandularis [25].

In our study the lesion was located in the infero posterior and right lateral surface of the bladder. He presented with macroscopic hematuia. CT scan showed a circumscribed fungating mass. Trans urethral resection was done. The histopathology report was Cystitis glandularis mucinous type. The patient did not have any complaints after one year follow up.

CONCLUSION

There are several histological variants of UB cancers, however SCC, mucinous adenocarcinoma and CCC are extremely rare. Extensive work-up including IHC studies are required to rule out any primary tumors and the possibility of metastasis, before confirming the diagnosis of these primary bladder tumors. Bladder paragangliomas are even more rare and majority are incidentally detected during investigation for hematuria or other lower urinary tract symptoms. Bladder paragangliomas require life long follow up to detect recurrence or metastasis.Isolated bladder NFs are extremely rare, which also requires follow up cystoscopic evaluation coupled with imaging studies to monitor potential recurrence or progression. Cystitis glandularis is a rare lesion of UB which is often mistaken as adenocarcinoma because of its deceiving cystoscopic and microscopic appearance. Cystitis glandularis is a chronic disease and should be considered as a distinct clinical entity.

Clinical suspicion and extensive studies are needed to confirm the diagnosis of these rare lesions.

Declaration by Authors

CONSENT

Written informed consents were obtained from the patients for publication of this article and accompanying images.

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