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Case Report

Pathology Section

Multifocal Urothelial Carcinoma Involving Renal Pelvis to Urinary Bladder: A Case Report

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ABSTRACT

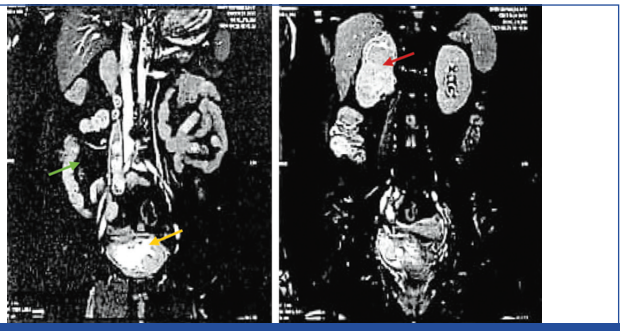
Urothelial carcinomas are malignancies arising from the lining epithelium of the urinary tract. It can develop anywhere starting from the renal pelvis to the urethra, involving the bladder and ureter in between. Multifocal occurrences as well as metachronous or synchronous recurrences have been reported in urothelial carcinoma, particularly in cases of upper tract urothelial carcinomas. Seeding of cancer cells and field cancerisation are two well explored hypotheses explaining the possible cause for such unique tumour characteristic. Here, we report a case of multifocal urothelial carcinoma in a 68-year-old female, presenting with carcinoma involving the renal pelvis, extending along the entire length of the ureter to finally infiltrate the bladder wall. Neo-adjuvant chemotherapy could not be administered due to poor renal function owing to hydronephrosis. Patient was surgically managed by radical nephrectoureterectomy and radical cystectomy. Postsurgery, resection margin of the specimen revealed microscopic evidence of residual neoplastic lesion of low malignant potential, necessitating the need for active long-term surveillance for possible recurrence. However, patient unfortunately succumbed to possible disease related health complications closely after surgery, preventing follow-up and further evaluation of the disease course. Synchronous bladder carcinoma with upper tract urothelial carcinoma is novel owing to its multifocality and an aggressive clinical course. Such a presentation of upper tract urothelial carcinoma indicates a simultaneous affliction of the entire urinary tract increasing the risk of residual disease and recurrence even with extensive radical surgery. Long-term aggressive follow-up is usually warranted in these cases to improve overall survival and cancer-specific survival.

Keywords: Field cancerisation, Metachronous, Progenitor cell, Synchronous, Upper tract urothelial carcinoma

CASE REPORT

A 68-year-old female presented with complaints of haematuria and lower flank pain for six months. Patient was diabetic and hypothyroid, on medication for around 15 years. Urine analysis revealed frank haematuria and 16-17 pus cells/high power field. Ultrasonography whole abdomen showed diffusely thickened urinary bladder wall along with right ureteric hydroureteronephrosis.

Magnetic Resonance Imaging (MRI) urography revealed moderate hydroureteronephrosis of right ureter with heterogenous mixed signal intensity contents in the pelvicalyceal system. Lobulated T2 hyperintense signal intensity mass was noted in the distal ureter extending till the level of vesicoureteric junction with length of distal ureteric involvement of about 10 cm. Another skip lesion was noted proximal to this lesion in the mid ureteric region measuring 1.3 cm in size. The urinary bladder was of normal contour, but showed a lobulated heterogenous mass lesion with central hyperintense areas of necrosis and eccentric diffusion on restriction [Table/Fig-1].



[Table/Fig-1]: MRI urography showing right renal hydronephrosis, hydroureteronephrosis, with heterogenous mixed signal intensity contents in the pelvicalyceal system (red arrow). Lobulated T2 hyperintense signal intensity mass noted in the distal ureter extending till the vesicoureteric junction (green arrow). The urinary bladder showed a lobulated heterogenous mass lesion with central hyperintense areas of necrosis (yellow arrow).

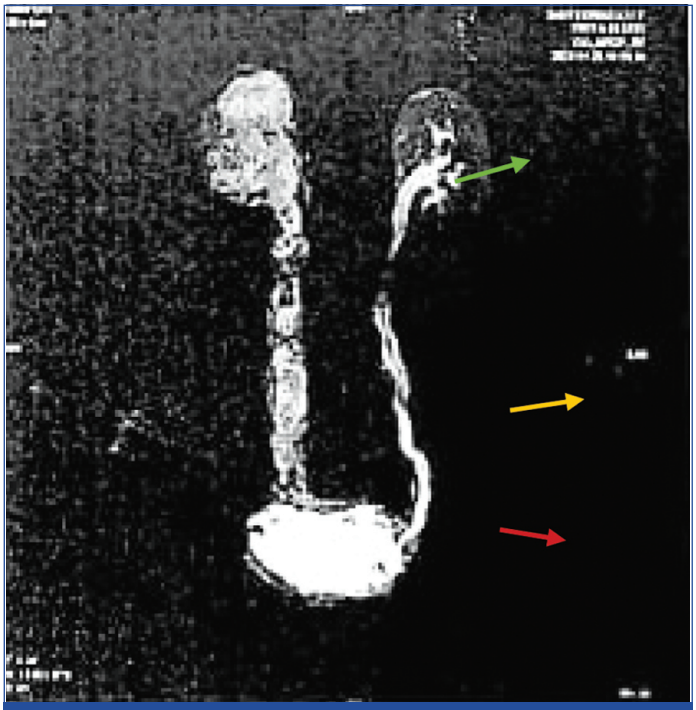
The MRI pelvis showed lobulated heterogenous mixed signal intensity mass lesion involving the bladder measuring (5x5.1) cm with central hyperintense areas of necrosis. The lesion showed eccentric areas of diffusion restriction [Table/Fig-2]. Screening of upper abdomen revealed mildly enlarged right kidney with ill-defined non-enhancing lobulated space occupying lesion involving the calyces, renal pelvis and right proximal ureter. Mild to moderately non-homogenously enhancing lobulated space occupying lesion was seen involving the distal half of the right ureter and extending down to the right vesicoureteric junction. There was also an ill-defined, non-homogenously enhancing space occupying lesion involving the entire urinary bladder circumferentially as well as the trigone, with a maximum wall thickness of 25 mm. Multifocal urothelial carcinoma was the provisional diagnosis, owing to the involvement of renal pelvis along with the ureter and the urinary bladder. Renal cell carcinoma with drop metastases to the bladder was a differential that was also considered.

Subsequently, patient underwent Transurethral Resection of Bladder Tumour (TURBT). Histopathological examination revealed low-grade invasive papillary urothelial carcinoma, focally infiltrating the lamina propria. Background urothelium showed evidence of urothelial dysplasia [Table/Fig-3].

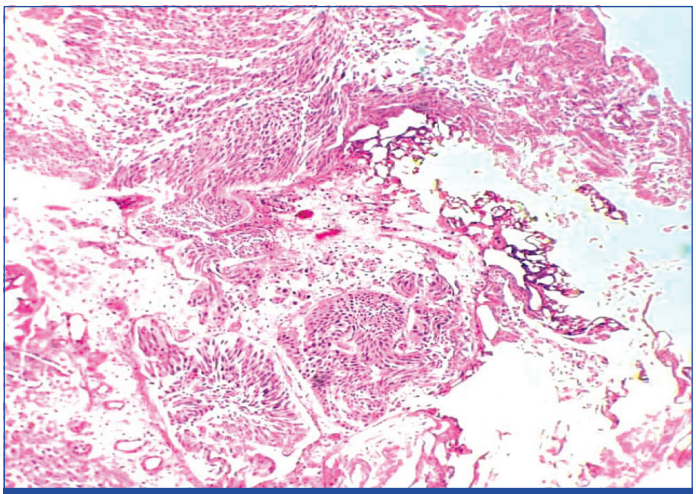
Patient was finally posted for right cysto-uretero-nephrectomy. Specimen comprised right nephrectoureterectomy with radical cystectomy in toto [Table/Fig-4]. Kidney was grossly hydronephrotic with a dilated pelvicalyceal system, filled by a friable, greyish-white necrotic tumour [Table/Fig-5]. Whole length of the ureter was occluded by a solid growth with papillary excrescences, without any serosal perforation [Table/Fig-6]. The bladder, on cut-section, showed a friable necrotic growth with papillary excrescences, filling up the entire lumen [Table/Fig-7].

Histopathological examination revealed invasive urothelial carcinoma, possibly arising from the renal pelvis. The tumour was predominantly

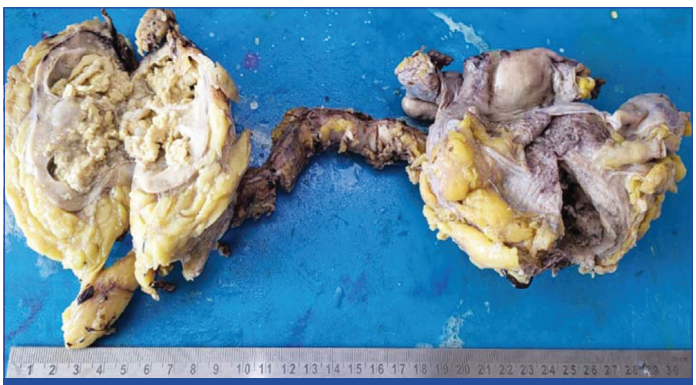
low-grade, with focal high-grade area. Infiltration was beyond the muscularis of renal pelvis, into the peri-ureteral, peri-pelvic fat and renal pelvis. The tumour was found to focally invade the lamina propria of bladder without detrusor muscle invasion. There was dysplasia of the background urothelium along with Papillary



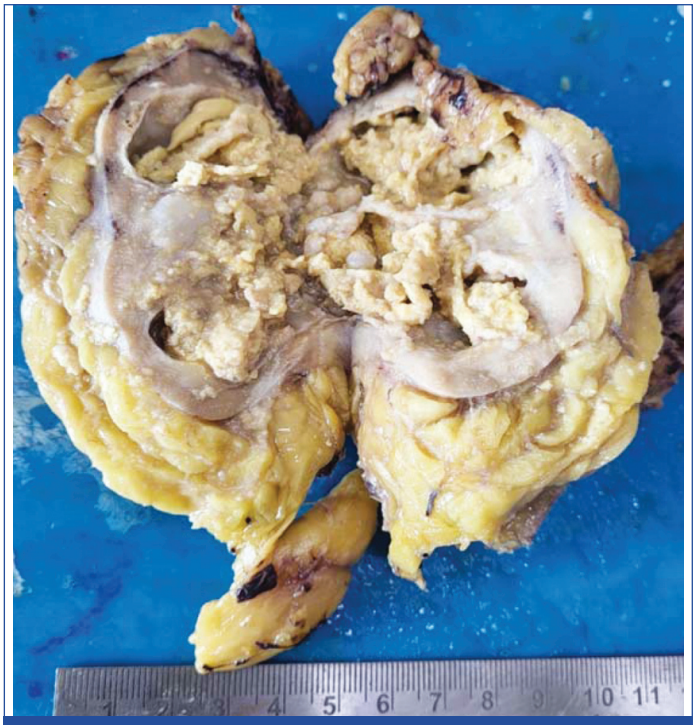
[Table/Fig-2]: MRI pelvis showing lobulated heterogenous mixed signal intensity mass lesion involving the bladder with central areas of necrosis (red arrow). Right kidney is enlarged with ill-defined non-enhancing lobulated space occupying lesion involving the calyces, renal pelvis and right proximal ureter (green arrow). Lobulated space occupying lesion involving the distal half of the right ureter upto the right vesico-ureteric junction (yellow arrow).



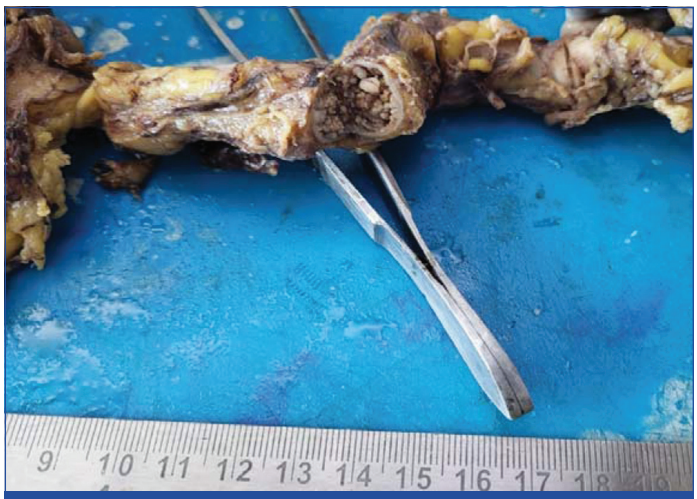
[Table/Fig-3]: Transurethral Resection of Bladder Tumour (TURBT) showing low-grade invasive papillary urothelial carcinoma, focally infiltrating the lamina propria (H&E, 20X).



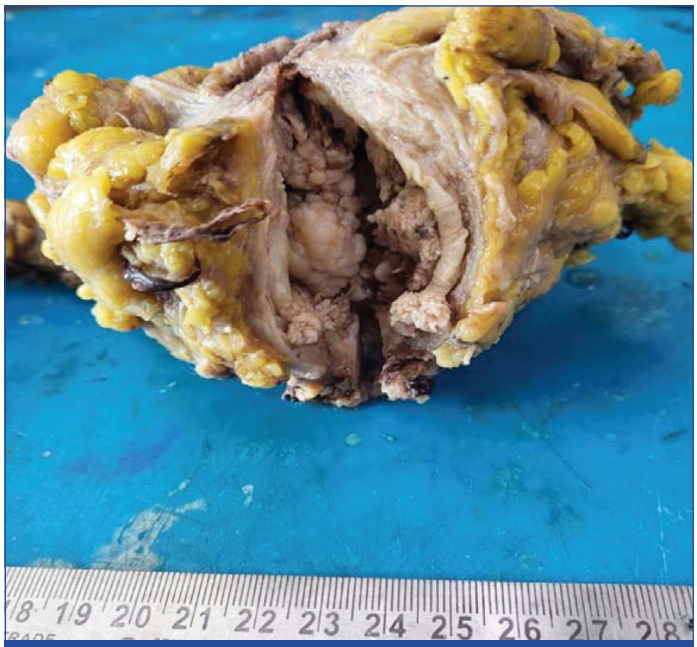
[Table/Fig-4]: Right nephrectoureterectomy with radical cystectomy comprising right kidney with right ureter and the urinary bladder removed en-bloc.



[Table/Fig-5]: Kidney was grossly hydronephrotic with a dilated pelvicalyceal system, filled by a friable, greyish-white necrotic tumour.

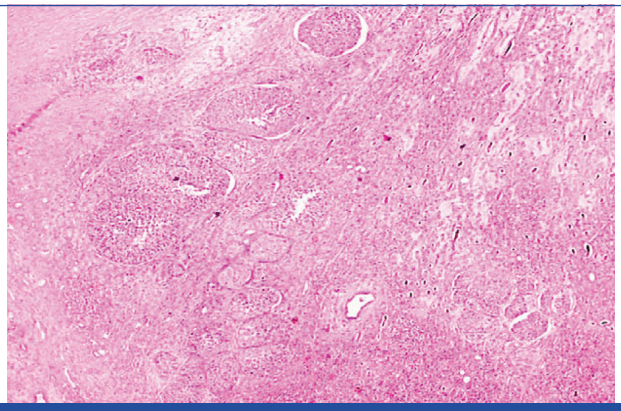


[Table/Fig-6]: Ureter was occluded by a solid growth with papillary excrescences, without any serosal perforation, along its entire length.

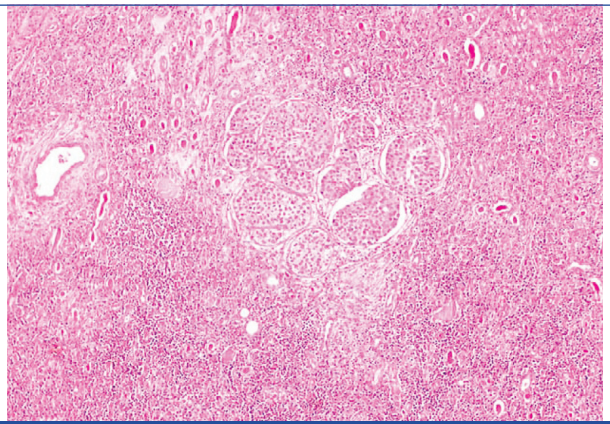


[Table/Fig-7]: The bladder showed a friable necrotic growth with papillary excrescences, filling up the entire lumen.

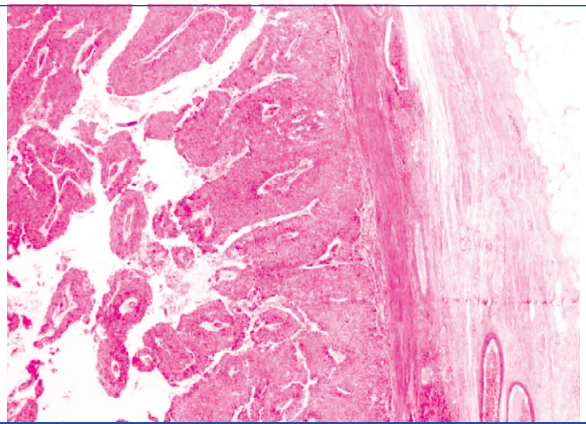
Urothelial Neoplasm of Low Malignant Potential (PUNLMP) of the urethral resection margin. The tumour measured 18 cm in maximum dimension and involved the entire length of the ureter with extension into the renal pelvis and the adjacent renal parenchyma along with infiltration into the bladder wall upto the lamina propria. No lymph nodes could be isolated from the renal hilar fat and also no regional lymph node was sent separately for histopathological evaluation by the surgeons. The tumour was staged pT3, pN not assigned. In view of the histopathological findings, it was concluded that it was a multifocal tumour, likely of renal pelvic/ureteric origin with synchronous involvement of the entire length of the ureter as well as the urinary bladder, possibly resulting from spread via a dysplastic urothelium along the entire urinary tract [Table/Fig-8-12]. The adjacent uninvolved renal parenchyma showed focal glomerulosclerosis and thyroidisation of renal tubules, suggestive of chronic pyelonephritis due to obstructive uropathy, arising from complete obliteration of renal pelvis and ureter by the tumour. The final histopathological diagnosis was multifocal urothelial carcinoma of renal pelvic/ureteric origin with synchronous involvement of the urinary bladder.



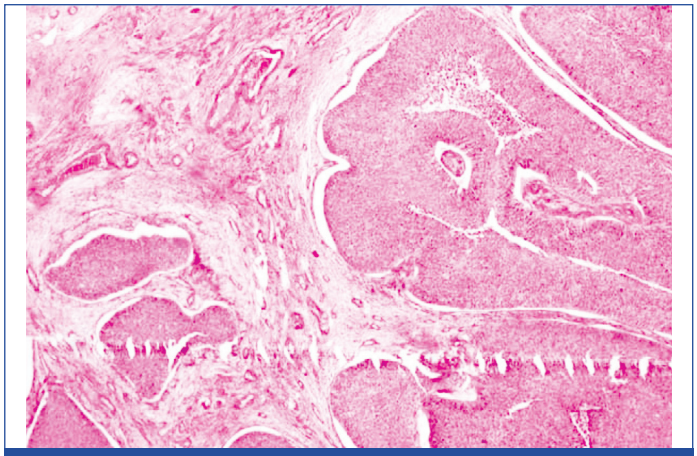
[Table/Fig-8]: Renal pelvic urothelial carcinoma invading beyond the muscularis of renal pelvis, into the peri-ureteral, peri-pelvic fat and renal parenchyma (H&E, 10X).



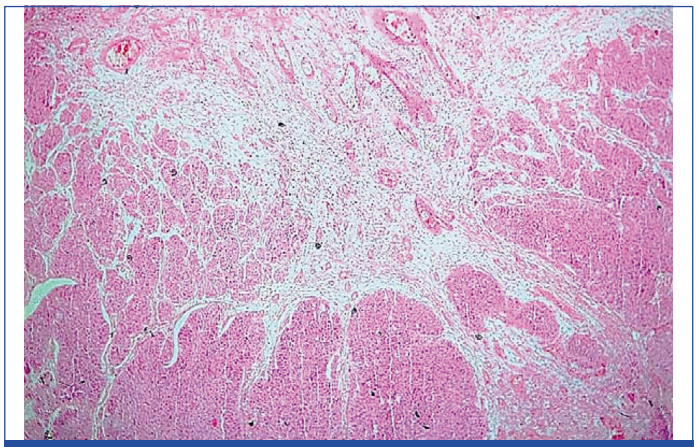
[Table/Fig-9]: Renal pelvic urothelial carcinoma invading beyond the muscularis of renal pelvis, into the peri-ureteral, peri-pelvic fat and renal parenchyma (H&E, 20X)



[Table/Fig-10]: Low-grade papillary urothelial carcinoma, non-invasive, involving the entire length of ureter (H&E, 10X).



[Table/Fig-11]: Low grade urothelial carcinoma, conventional, infiltrating the lamina propria of the urinary bladder.



[Table/Fig-12]: Low grade urothelial carcinoma, conventional, infiltrating the lamina propria of urinary bladder (H&E, 20X).

Postoperative stay at the hospital was unremarkable. Patient was kept on active surveillance and follow-up in the postsurgical period. Adjuvant chemotherapy could not be administered to the patient due to poor renal function. However, patient was brought to the emergency department after six months in an unresponsive state and unfortunately, could not be revived with resuscitative measures.

DISCUSSION

As per GLOBOCAN 2022 data, urothelial carcinoma is the 9th most common cancer globally with 614,298 new reported cases [1]. Upper tract urothelial carcinomas, arising from the renal pelvis and ureter, are relatively uncommon entity with an incidence of around 5-10% of all urothelial carcinomas [2]. Multifocal development is a feature of urothelial carcinoma, both synchronously as well as metachronously. Incidence of synchronous urothelial carcinoma of the bladder at the time of diagnosis of upper urinary tract urothelial carcinoma is estimated to be around 17% [3]. Multifocality has been explained by two hypotheses, seeding of cancer cells in the urinary tract or by the process of field cancerisation [4].

There are two proposed hypotheses for the multifocal development of urothelial carcinoma. One is the “field cancerisation” hypothesis, where there is priming of the urothelial cells by carcinogenic insults leading to their transformation. The second hypothesis is “Single progenitor cell hypothesis” stating that the genetic and phenotypic heterogeneity results from the clonal expansion of a single transformed cell [5]. Dysplasia or carcinoma in situ, frequently identified around or distant from the main tumour supports the concept of field cancerisation [6,7]. However, various molecular analyses have supported the concept of single clonal cell. Sidransky D et al., found that the same X-chromosome allele was inactivated in all the tumours in a single bladder, in four female cases of multiple bladder tumours [8]. Lunec J et al., and Habuchi T et al., found identical mutation

sites and patterns of p53 gene alterations in cases of heterotopic synchronous or recurrent urothelial carcinomas of bladder or the upper urothelial tracts [9,10]. Monoclonal origin and intraepithelial spread have been observed by Simon R et al., where comparative genomic hybridisation in 32 bladder tumours showed identical TP53 mutations and protein overexpressions in tumours of same individual and also in the mucosal samples from the continuous areas [11].

Rare occurrence of upper urinary tract carcinomas after transurethral resections of bladder carcinomas are seen most frequently in patients with vesicoureteral reflux, supporting the concept of seeding or implantation of primary urothelial cancer cells by spreading via the urine rather than field cancerisation [12]. The two hypotheses continue to be discussed in the aetiology of multifocality, clonal expansion following intraluminal spread being the most frequent explanation for multifocality.

Aparna DR et al., reported a case of synchronous urothelial carcinomas involving the renal pelvis and the urinary bladder [13]. Zhang JQ et al., reported a case of metachronous urothelial carcinoma in the renal pelvis and the urethra [14]. Nangia A et al., also reported multifocal sarcomatoid urothelial carcinoma involving the renal pelvis, pelviureteric junction along with the entire length of the ureter [15].

Synchronous bladder carcinomas at the time of diagnosis of upper tract urothelial carcinomas usually represent an advanced stage aggressive malignancy. Hence, neoadjuvant chemotherapy before radical surgery is usually the treatment of choice [16]. Radical surgery, however, was considered upfront in our patient due to worsening renal functions owing to hydronephrosis, making her an unsuitable candidate for potentially nephrotoxic chemotherapeutic agents. Long-term follow-up is essential for patients with urothelial carcinomas involving anywhere along the upper or lower urinary tracts. Elawdy MM et al., in their retrospective study of 275 cases of upper tract urothelial carcinoma reported a prevalence of recurrence in the bladder of 46%, urethra of 2%, contralateral recurrence of 1%, distant metastasis of 7.5% and local metastasis of 6%. They concluded that upper tract urothelial carcinomas were capable of synchronous as well as metachronous recurrences and hence required long-term surveillance [17].

In our present case, radiological evidence of lesion involving the bladder and entire length of the ureter along with renal involvement limited to the renal pelvis and calyces was highly suggestive of urothelial origin of the tumour. However, a second differential considered initially, prior to histopathological evaluation of the bladder tumour was renal cell carcinoma with drop metastases to the bladder. Synchronous primaries of the kidney and the urinary bladder were the least likely differential in the present case.

CONCLUSION(S)

Upper tract urothelial carcinomas are relatively rare tumours. These tumours are unique in their frequent association with multicentric occurrence and synchronous as well as metachronous recurrences. Multifocality and downstream seeding of malignant cells from upper tract urothelial carcinoma necessitates long term for long term intense surveillance for metastases and recurrences. In our study, microscopic examination of nephrecto-ureterectomy and radical cystectomy revealed the presence of a urothelial neoplasm of low malignant potential in the resection margin, indicating a residual neoplastic process in the downstream urothelial lining, despite a radical resection surgery. Hence, it was concluded that upper tract urothelial carcinomas tend to show a propensity for spreading to downstream tissues along the dysplastic urothelial lining.

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