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ORIGINAL RESEARCH

Clinico-pathological profile of upper tract urothelial carcinoma, a tertiary care hospital experience

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ABSTRACT

Background: Upper Tract Urothelial Carcinoma (UTUC) is a rare tumor originating anywhere, from the renal calyces to the ureteric orifices. **Methods:** We intended to observe the demographical and clinico-pathological features of UTUC patients in our hospital. **Results:** 20 patients of UTUC with median age of 44.7±9.25 years , male to female ratio of 5.7 were studied for a follow up period of 6 months. Majority of the patients 13(65.0%) presented with painless gross hematuria. All UTUC patients 20(100%) had pre-operative hydronephrosis, 13(65%) were smokers. The most common comorbidity in our patients was hypertension. 12(60%) and 7(35%) patients were diabetics. Open nephroureterectomy was done in all patients. The average maximum size of UTUC was 4.1cm range (2-10cm). Most of the patients 10(50%) had stage II disease followed by stage III & IV in 7(35.0%) and 3(5.0%) patients respectively. There was a preponderance of papillary morphology 12(60.0%) in our patients. 95.0% of the patients had high grade tumors. **Conclusion**: In addition to having an excellent back up from radiology, pathology and medical oncology,it is important to know the epidemiology, natural history, genetics and etiological risk factors for this malignancy so thatnew modalities may be explored to reduce diagnostic challenges and improve patient management

Keywords: Upper TractUrothelial Carcinoma (UTUC), Bladder,Ureter, Tumor, Nephroureterectomy

INTRODUCTION

Upper Tract Urothelial Carcinomas (UTUC) are relatively rare tumors, with an estimated incidence of 1 to 2 cases per 100,000 individuals per year[1,2,3]. UTUCs comprise urothelial carcinomas originating anywhere from the renal calyces to the ureteric orifices. Tumors arising from within the renal pelvis occur four times more commonly than ureteric lesions. In comparison to Lower Tract Urothelial Carcinoma (LTUC), UTUCs are less common, representing only 5-10% of all urothelial cancers[4]. At present, both tumor types are grouped together in the tumor, nodes, metastasis (TNM) classification system as UTUC[3,4,5]. UTUC is histologically similar to LTUC yet several clinical, biological and molecular features are unique to UTUC, prompting the term disparate twins when considering the similarities and differences between UTUC and LTUC[6]. Major knowledge gaps remain in our understanding of the biology and genomic landscape of UTUC, a rare disease in Western countries but of potentially epidemic proportions in the Far East[7]. Biologically interesting features along the environmental-genetic spectrum include the strong association between known exposure to agents such as tobacco[8] and genetic predisposition[9,10]. UTUC is a clinically heterogenous disease with a varied natural history, and given its location in the upper urinary tract, treatment has the potential to cause or worsen chronic kidney disease. Accordingly, physicians caring for UTUC patients must be well accustomed with multiple diagnostic and therapeutic tools in order to provide optimal patient care[11].In this study we intended to observe the demographical and clinico-pathological features of UTUC patients who underwent radical surgery for in our hospital.

METHODS

A prospective observational study was conducted between 15thJune 2019 to 20 September 2022 in the department of urology and pathology at Park advanced specialty hospital and Paras Hospital in Delhi NCR. After obtaining institutional ethics committee approval, all patients with no age bar and

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of any gender who underwent radical nephroureterectomy for UTUC were included in our study. We recorded the demographic, clinical and pathological features of 21 patients after obtaining an informed consent. Patients harboring past history of any other malignancy, and those who declined consent were excluded from the study. CECT chest abdomen and pelvis was utilized for diagnosis and staging of disease. Preoperative ureteroscopy was done in selective patients. Cancer staging was done as per TNM staging 8th edition and risk stratification as per latest EUA guidelines.(Table 1)

All the patients in our study belonged to high-risk group (EAU guidelines 2021) and underwent open radical nephro-ureterectomy. All patients received intravesicalMytomycin C within 2-5 days postoperatively after performing a cystogram. Further treatment of these patients was dictated by histopathological examination and the performance status. Regular follow up was made weekly for first four weeks and then monthly till six months after definitive surgical procedure. Thereafter, patients were followed three monthly. Cystoscopy and CECT chest/abdomen/pelvis were done during follow up as per protocol or earlier when needed.Demographic data are given as medians (range), whereas the other data are expressed as mean ± SD. Data were analyzedusing statistical software (SPSS for windows 10.0; SPSS, Chicago, IL, USA).

RESULTS

The study included a total of 20 UTUC patients. The median age ±SD was 44.7±9.25.There were 17(85%) males and 3(15%) females in our study population. Majority of the patients 13(65.0%) presented with painless gross hematuria, 3(15%) patients presented with Gross hematuria with clot colic and 2(10.0%) of patients were diagnosed incidentally, whereas equal number of patients had pyonephrosis at presentation. All UTUC patients 20(100%) had pre-operative hydronephrosis, 13(65%) were smokers (**Table 2**). The most common comorbidity in our patients was hypertension. 12(60%) patients were hypertensive on medication and 7(35%) patients were diabetics on insulin or oral hypoglycemic agents, 1(5%) patient had hypothyroidism. The average maximum size of UTUC was 4.1cm range (2-10cm). Most of the patients 10(50%) had stage II disease followed by stage III & IV in 7(35.0%) and 3(5.0%) patients respectively. There was a preponderance of papillary morphology 12(60.0%) in our series of patients (**Figure 2**) followed by ulceroinfiltrative morphology in 5(25%) and solid in 3(15.0%) patients. Majority of the patients 19(95.0%) had high grade tumors (Figure 3a,3b). Only one had low grade pathology (Figure 3c,3d). All the patients in our study underwent open radical nephro-ureterectomy under general anesthesia. Furthermore, no major early complication was recorded in any of the patients enrolled in our study (**table 3**). All the patients were regularly followed up. The minimum follow up period was 6 months. During the course of this study, bladder recurrence was reported in 4(6.0%) patients. There was no mortality in our study.

Table 1: EAU risk stratification of non-metastatic UTUC

Low-risk UTUC (all criteria must be present)	High-risk UTUC (any criteria may be present)
Unifocal disease	Hydronephrosis
Tumor size <2 cm	Tumor size >2 cm
Low-grade cytology	High-grade cytology
Low-grade biopsy	High-grade biopsy
No invasive aspect on imaging	Multifocal disease
	Previous radical cystectomy for bladder cancer
	Variant histology

Table 2: Demographic and pathological profile of UTUC patients

S. No	Parameter		Number of patients (n=20)	Percentage
1	Age	<50	7	35
		>50	13	65
2	Gender	Male	17	85
		Female	3	15
3	Smoking status	Yes	13	65
		No	7	35
4	Pesticide exposure	Yes	12	60
		No	8	40
5	Grade	Low grade	2	10
		High grade	18	90
6	Stage	T1	2	10
		T2	18	90

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Table 3: Complication profile in UTUC patients

S.No	Complications		Number of patients(n=20)	Percentage
1	Early complications	None	10	50
		Fever	2	10
		Pneumonia	1	5
		Postoperative wound infection	2	10
		Sepsis	1	5
		Adrenal insufficiency	1	5
2	Late complications	Bladder recurrence	4	20
		Skeletal metastasis	0	0

Figure 1: shows multifocal papillary growth in pelvis and ureter with a staghorn calculus in pelvis

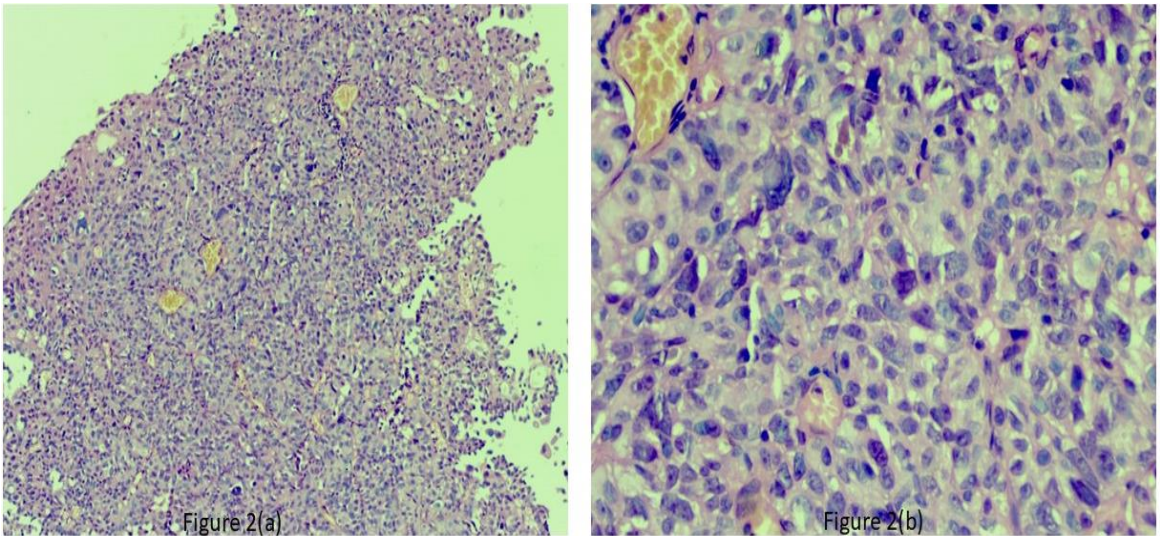

Figure 2(a) shows low power view of high grade urothelial carcinoma, 2(b) high power of same case showing marked nuclear atypia with hyperchromatic nuclei.

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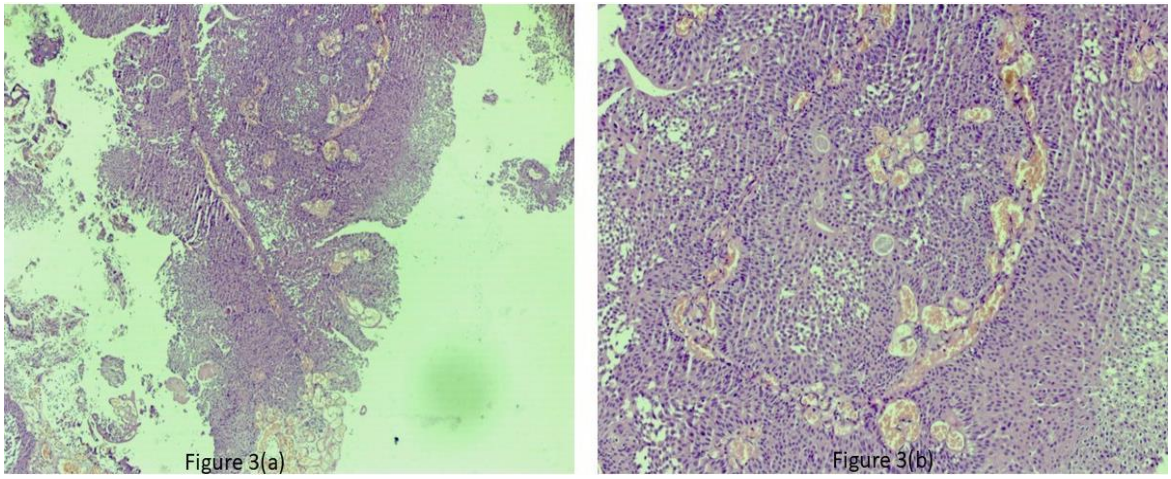

Figure 3 (a) shows low power view of low grade papillary urothelial carcinoma, 3(b) showing high power view with fused papillae and minimal loss of polarity.

DISCUSSION

Urothelial carcinoma is a pan-urothelial disease i.e. it may affect urothelialcells at any site on the luminal surface of the urinary tract extendingfrom renal calyces to the proximal urethra. Furthermore, many UCCs aremultifocal and synchronous tumors that can be detected both in the bladder andin the upper tracts at initial presentation[12,13]. The possibility of developing synchronous,multifocal urothelial carcinoma in the urinary tract may be explained by twotheories: The first is the 'Field Change theory'[14] in whichthe multifocal development of cancer is secondary to the continuous exposureof the urothelium to carcinogens in the urine and the second is the 'cancer cellseeding theory[15]' in which multiple carcinomas are theresult of intraluminal spread from a single lesion.

UTUC is uncommon malignancy with an annual incidence of 0.7/100000 population in US population. UTUC constituted 28.6 percent cases of our study cohort. In line with the available literature, a male to female ratio was 5.6.This is presumed firstly because of an increased prevalence of smoking and exposure to environmental toxins[16,17]. Secondly It has been hypothesized that the cellular metabolism ofcarcinogens may be different in men as compared to women[18]. Metabolic enzymes including 5"-diphosphoglucuro-nosyltransferase (UGT), which is involved in aromatic amine metabolism, and glutathione-S-transferase M1 (GSTM1), involved in foreign substance detoxificationhave been implicated in bladder cancer–associated carcinogen metabolism. Both enzymes have been shown to be differentially expressed in men and women[19,20.] In addition, gender differences have been explained by differences in sex steroid production and receptor expression.71 % of our study population were tobacco smokers. Tobacco is the main known cause of urothelial carcinoma (30% to 40%). Smokers have a 2- to 3-fold increased risk of bladdercancer[21]which is at par with the literature. Smoking exposure is complex in terms of mechanism of action for carcino-genesis. A variety of toxic substances are inhaled during smoking and include aromatic amine with arylamine, benzopyrene, and dimethylbenzanthracene. These aromatic amines are metabolized by the body in the carcinogenic N-hydroxylamine. The detoxification of this derivative takes place by severalenzyme systems (cytochrome P450s with CYP1A1, glutathione S-transferases, and N-acetyl transferases). Genetic polymorphisms in enzymes that neutralize N-hydroxylamine may reflect susceptibility to the carcinogenic effect ofsmoking. Preoperatively, hydronephrosis was observed in all UTUC patients.

Being elderly and smokers, almost half of our study population had one or more comorbidities. Hypertension and diabetes were the most common medical conditions observed in our cohort.Patients having UTUC were all high risk and underwent open radical nephroureterectomy. Histopathological examination demonstrated 100% ofpatients having deeply invasive disease. UTUC are significantly moreaggressive and deeply invasive than UBUC. Among UBUC patients, the expression pattern was comparable between the T1 & T2 tumor stage, whereas, in the UTUC group, majority of thepatients present with T2 stage Although this has been alluded topreviously, this difference has not, until now, been well established[22,23].The more aggressive nature of upper urinarytract cancer might be a consequence of the higher grade lesions found, or mightrepresent anatomical differences between the bladder and ureter or renal pelvisand earlier transmural spread.

Being a rare entity, most of the data about UTUC is retrospective. However, this study presents a good sample of UTUC patients underlining their demographical and clinico-pathological features prospectively. The limitations in our study include poor long term follow up and small sample size. Moreover, minimally invasive techniques of surgery like robotic and laparoscopy would certainly help improving the complication profile of our study cohort.

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CONCLUSIONS

Being a rare disease UTUC is difficult to diagnose and manage for urologists. An excellent radiological and pathological backup is absolutely essential to make out the diagnosis and medical oncology team for providing accurate treatment as per the stage and risk strata. Moreover, it is important to know the epidemiology, natural history, genetics and etiological risk factors for this malignancy. An in-depth knowledge about the imaging/pathologic limitations, patient comorbidities, and risk stratification tools will help us develop new modalities to reduce diagnostic challenges and improve patient management.

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