

Histologic Variants of Urothelial Carcinoma: A Retrospective Study of Cystoscopic Biopsies

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Abstract

Background: Urothelial carcinoma is the most common malignancy of the urinary tract. Many variants of infiltrating urothelial carcinoma have been described which are aggressive tumors associated with advanced disease at presentation and are often managed with neoadjuvant chemotherapy and radical cystectomy. **Material and Methods:** 56 TURBT specimens received in the department of Pathology, ASCOMS and hospital were included in the study. All the specimens were fixed in 10% buffered formalin, paraffin sections and stained with Hematoxylin-Eosin stain. Histological analysis of the slides was carried out. Relevant clinical data regarding age and sex was recorded. **Results:** 56 TURBT biopsies were analyzed. Male to female ratio was 3.6:1. Mean age of patients was 60.79 years with a range of 35-90 years. Out of 56 cases of urothelial carcinomas, 57.14% were high grade and 42.85% low grade. 60.71% carcinomas showed pT1, 32.14% pT2 and 7.14% pTa stage. Pure urothelial carcinoma was noted in 69.64%, with squamous differentiation in 19.64%, glandular differentiation in 5.35%. One case each (1.78%) of sarcomatoid, plasmacytoid and nested variant was seen. All the infiltrating urothelial carcinomas with variant morphologies presented in pT2 stage except 3 tumors with squamous differentiation in pT1. **Conclusion:** Urothelial carcinoma is a common malignant tumor of urinary bladder

Key Words

Urothelial carcinoma, Squamous cell carcinoma, Adenocarcinoma

Introduction

The most common malignancy of the urinary tract is bladder cancer. It is the 9th most common malignancy worldwide. [1] Various types of bladder cancers include urothelial carcinoma, squamous cell carcinoma and adenocarcinoma. Urothelial carcinoma consists of 90% of all primary tumors of urinary bladder. [2]. There are multiple risk factors, most important include cigarette smoking and occupational exposure. Other factors can be long term analgesic use and anti-cancer drugs.

Schistosoma hematobium is the main cause of squamous cell carcinoma in developing countries. [3] The most critical aspect of diagnosing urothelial carcinoma is the recognition of invasion because the management and prognosis are significantly different between invasive and noninvasive tumors. Although most infiltrating urothelial carcinomas manifest conventional morphology and the evaluation of invasion is usually straightforward, the diagnosis of the

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relatively rare histologic variants of urothelial carcinoma and their patterns of invasion may be a challenging task. Recognizing urothelial carcinoma with variant morphologic components is important because of the differences in clinical behavior, which have different management and may predict a different prognosis.

The World Health Organization 2016 system is currently applied for classification, grading and staging of urothelial carcinomas. The tumors are graded into two categories-low grade (LG) and high grade (HG) based on cytological and architectural features. Non-invasive papillary urothelial carcinoma is designated as pTa; while stages pT1, pT2, pT3 and pT4 refer to invasion into the lamina propria, muscularis propria, perivesical tissue and adjacent organs respectively. Non-invasive urothelial carcinoma i.e. carcinoma-in-situ is stage Tis.^[4]

Material and Methods

The study was carried out in the department of Pathology, Acharya Shri Chander College of Medical Sciences and Hospital (ASCOMS) and hospital, Jammu. 56 transurethral resection (TURBT) specimens received over a period of 2 years were studied. The specimens were fixed in 10% buffered formalin; 4-6 μ paraffin sections were cut and stained with Hematoxylin and Eosin (H&E) stain. Histopathological slides of the specimens were reviewed under light microscope. Microscopic analyses were carried out, variants of urothelial carcinoma were analyzed and tumors were graded and staged according to WHO, 2016. Relevant clinical data regarding age and sex was recorded.

Results

In our study, 56 TURBT biopsies were analyzed. Among these, 44 (78.6%) were males and 12 (21.4%) were females. Male to female ratio being 3.6:1. Age range was 35-90 with mean age of 60.79 years and peak incidence in 61-70 years age group (Table 1).

Out of 56 cases of urothelial carcinomas, 32 (57.14%) were of high grade (Fig 1) and 24 (42.85%) cases were of low grade.

Table 2 depicts grading and staging of urothelial carcinoma. Among low grade carcinomas, 20 (83.33%) belonged to stage pT1 and the remaining 4 (16.67%) cases were non-invasive (pTa). High grade tumors showed higher stage pT2 in 18 (56.25%) and pT1 in 14 (43.75%) patients. Out of 11 infiltrating urothelial carcinomas with squamous differentiation, only 3 were in pT1 stage whereas rest of the 8 cases were muscle invasive (pT2). All the other variants comprised pT2 stage tumors.

Table 3 shows histological variants of urinary bladder carcinoma.

Squamous differentiation was seen in 11 cases, 3 cases presented with glandular differentiation and 1 case each consisted of sarcomatoid, plasmacytoid and nested variant.

The most common histologic variant of urothelial carcinoma (19.64%) was with squamous differentiation, followed by glandular differentiation (5.35%). Squamous differentiation was characterized by nests of malignant polygonal cells often showing keratinization with keratin pearl formation (Fig 2). Some of the areas of the tumor exhibited clear cell features (Fig 3). Glandular differentiation depicted true glandular spaces within urothelial carcinoma (Fig 4). Other variants of infiltrating urothelial carcinomas constituted a single case of sarcomatoid, plasmacytoid and nested type. Sarcomatoid variant showed biphasic malignant tumor (Fig 5) with areas of heterologous differentiation with bone formation (Fig 6). In plasmacytoid variant, tumor was composed of cells having eccentric nuclei and abundant eosinophilic cytoplasm (Fig 7). The nested variant shows nested growth pattern of benign looking cells with scattered more atypical cells (Fig 8).

Discussion

The study comprised histopathological evaluation of 56 TURBT specimens. The male to female ratio was 3.6:1. Hasan *et al*^[5] and Cheng *et al*^[6] in their studies of bladder cancer reported male to female ratio of 2.58:1 and 3.3:1.0 respectively. Lim *et al*^[7] found male to female ratio of 5:1 in their study.

In our study the most common age group was 61-70 years with 35.7% cases which was compatible with a study by Vaidya *et al* of 33.73% cases in 61-70 years.^[8] Mean age of presentation in our study was 60.79 years which is in agreement with a study by Matalka *et al*^[9] in which mean age of the patients was 60.6 years.

Bladder cancer can be classified histologically as urothelial or non-urothelial. Urothelial cancer has a propensity for divergent differentiation. The recent World Health Organization classification of invasive urothelial cancers (2016), improved clarity on this issue, with its listing of 13 histologic variants of urothelial cancer. The divergent differentiation patterns include, amongst others, squamous, glandular, micropapillary, nested, lymphoepithelioma-like, plasmacytoid and sarcomatoid variants of urothelial cancer. Mostly, the current evidence suggests that urothelial cancer with divergent differentiation has a worse prognosis when compared

Table 1. Age distribution of the patients(N=56)

Age (Years)	No. of Cases	Percentage
35-40	04	7.14%
41-50	02	3.57%
51-60	12	21.42%
61-70	20	35.71%
71-80	16	28.57%
81-90	02	3.57%
TOTAL	56	

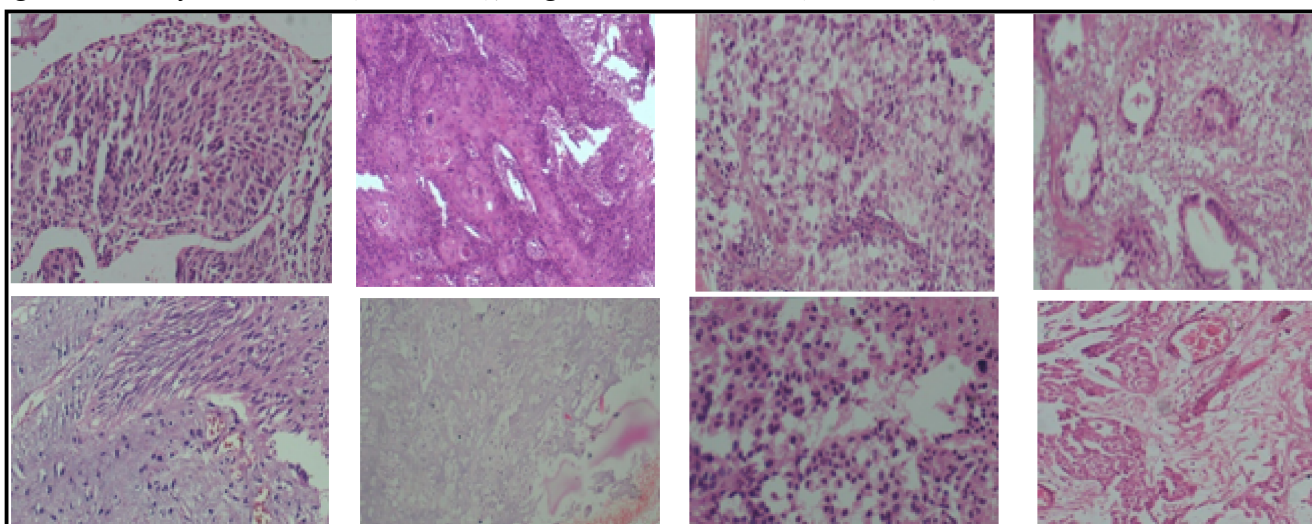
Table 2. Grade and Stage of Carcinoma

GRADE	STAGE			
	pTa	pT1	pT2	Total
Low grade	4	20	0	24
High grade	0	14	18	32
Total	4	34	18	56

Table 3. Histological classification of urinary bladder carcinoma(N=56)

Histological Type	Variant	No. of Cases	Percentage
Urothelial carcinoma	Pure urothelial carcinoma	39	69.64%
	Squamous diff.	11	19.64%
	Glandular diff.	03	5.35%
	Sarcomatoid variant	01	1.78%
	Plasmacytoid variant	01	1.78%
	Nested variant	01	1.78%

Fig. 1 High grade urothelial carcinoma (H&Ex400); Fig. 2 Squamous differentiation (H&Ex400); Fig. 3 Clear cell change (H&Ex100); Fig. 4 Glandular differentiation (H&Ex400); Fig. 5Sarcomatoid carcinoma with biphasic pattern (H&Ex400); Fig. 6Sarcomatoid carcinoma with heterologous bone formation (H&Ex100); Fig. 7 Plasmacytoid variant (H&Ex400); Fig. 8 Nested variant (H&Ex400).



with pure urothelial cancer.^[10] Squamous differentiation is the most common variant of urothelial cancer, with recent reports noting its presence in 16.8% to 22.1% of

cases.^[11] In our study we found pure urothelial carcinoma was seen in 69.64% cases and with squamous differentiation in 19.64%. Antunes and colleagues analyzed the outcomes of 113 patients treated with radical cystectomy. They found squamous differentiation, present in 22.1% of cases, was an independent predictor of cancer specific survival.^[11] The main differential diagnosis of this variant is pure squamous cell carcinoma. Careful sampling is important to identify an urothelial carcinoma component, either

invasive or in-situ. Glandular differentiation in our study was seen in 5.35% of cases. Glandular differentiation is an infrequent variant of urothelial cancer, with an incidence

of up to 16%^[12]. Predominance of glandular component may have worse prognosis, than tumors with limited adenocarcinoma pattern. Recognition of both urothelial and glandular components is important to make correct diagnosis and differentiate it from pure adenocarcinoma, either primary or metastatic.

Other variants of urothelial carcinoma are rare.^[13-15] A solitary case each of sarcomatoid, plasmacytoid and nested variant was present in our series. It is important to recognize histological variants of urothelial carcinoma as they indicate aggressive disease. Diagnosis can pose challenges due to sampling limitations and inter observer variability. Although associated with advanced disease at presentation, with appropriate treatment, survival outcomes are not significantly different compared with pure urothelial carcinoma of the same stage.^[16] Most of the cases in our study with aberrant differentiation and variant histology belonged to higher grade and pathological stage.

Conclusion

Urothelial carcinoma is a common malignant tumor of urinary bladder. It displays many variant morphologic appearances, which pose diagnostic challenge and have aggressive behavior. Recognition of divergent differentiation and variants of infiltrating urothelial carcinoma is essential because of implications for management and prognosis.

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Conflicts of Interest

There are no conflicts of interest.

References

1. Ploeg M, Aben KK, Kiemeny LA. The present and future burden of urinary bladder cancer in the world. *World J Urol* 2009; 27:289.
2. Kumar MU, Yelkar BR. Spectrum of Lesions in Cystoscopic Bladder Biopsies - A Histopathological Study. *Al Ameen J Med Sci* 2012; 5(2): 132-6.
3. Nagy AA, Darweish H, Hamdey HM, Elkalla R, Abdallah H, *et al.* Factors Affecting Survival in Egyptian Patients Suffering from Urinary Bladder Cancer: A Multicenter Retrospective Study. *J Cancer Sci Ther* 2018; 10: 31-5.
4. Moch H, Humphrey PA, Ulbright TM, Reuter VE. WHO Classification of Tumours of the Urinary System and Male Genital Organs. IN: H. Moch. WHO Classification of Tumours of the Urinary System and Male Genital Organs. Lyon, France. IARC Press; Lyon, France; 2016.
5. Hasan SM, Imtiaz F. Frequency of transitional cell carcinoma in local suburban population of Karachi. *JLUMHS* 2007; 12: 83-85.
6. Cheng L, Pan CX, Yang XJ, Lopez-Beltran A, MacLennan GT. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. *Cancer* 2004; 101(5):957-62.
7. Lim M, Adsay NV, Grignon D, Osunkoya AO. Urothelial carcinoma with villoglandular differentiation: a study of 14 cases. *Mod Pathol* 2009; 22(10):1280-6.
8. Vaidya S, Lakhey M, Sabira KC, Hirachand S. Urothelial tumors of the urinary bladder: A histopathological study of cystoscopic biopsies. *J Nepal Med Assoc* 2013; 52(191): 475-8.
9. Matalka I, Bani-Hani K, Shotar A, Bani-Hani O, Bani-Hani I. Transitional cell carcinoma of the urinary bladder: a clinicopathological study. *Singapore Med J* 2008; 49(10):790-4.
10. Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. *Can Urol Assoc J* 2009; 3(6 Suppl 4): 193-8.
11. Antunes AA, Nesrallah LJ, Dall'Oglio MF, Maluf CE, Camara C, Letie KR, *et al.* The role of squamous differentiation in patients with transitional cell carcinoma of the bladder treated with radical cystectomy. *Int Braz J Urol* 2007; 33(3):339-45; 339-45.
12. Domanowska E, Jozwicki W, Domaniewski J, Golda R, Skok Z, Wisniewska H, *et al.* Muscle-invasive urothelial cell carcinoma of the human bladder: Multidirectional differentiation and ability to metastasize. *Hum Pathol* 2007; 38:741-6.
13. Daga G, Kerkar P. Sarcomatoid carcinoma of urinary bladder: a case report. *Indian J Surg Oncol* 2018; 9(4):644-8.
14. Zeeba S, Jairajpuri, Safia R, Ali MA, Jetley S. Plasmacytoid variant of urothelial carcinoma: Diagnostic challenges and role of immunohistochemistry. *Int J Appl Basic Med Res* 2015; 5(3):217-9.
15. Krishnamoorthy S, Korula A, Kekre NS. The nested variant of transitional carcinoma of urinary bladder: An aggressive tumour with a bland morphology. *Indian J Urol* 2006; 22(4):378-80.
16. Lobo N, Shariat SF, Guo CC, Fernandez MI, Kassouf W, Chowdhury A *et al.* What is the significance of variant histology in urothelial carcinoma Review. *Bladder Cancer* 2020; 6(4):653-8.