International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Original Research Article.

Study of Cytomorphological Features of Low-Grade Urothelial Carcinoma And Spectrum of Bladder Tumors Diagnosed on Voided Urine Cytology

Namrata Aggarwal[1], Vijeta Tomar[1*], Nitin Negi[2]

[1]**Assistant Professor, Department of Pathology, S. M. S. Medical College, Jaipur, Rajasthan, India.**
[2]**Consultant and Head, Department of Urology, Metro MAS Hospital, Jaipur, Rajasthan, India.**

ABSTRACT

Background: Urothelial carcinoma of the bladder is the 7th most common cancer. Urine cytology is useful for the diagnosis and follow up of high-grade urothelial carcinoma (HGUC). However, its use in diagnosing low grade urothelial carcinoma (LGUC) remains controversial because of its low sensitivity.

Aim: To study the cytomorphology of LGUC in voided urine samples and spectrum of bladder tumors diagnosed on voided urine cytology.

Materials and Methods: This is a prospective study of two years, including 96 voided urine samples in a tertiary care centre. The urine cytology smears were stained with H & E stain were examined & critically analyzed for cytomorphological features and were categorised.

Results: Out of 96 cases studied, 30 cases were of HGUC, 19 of LGUC, 33 were found to be negative for malignant cells, 8 were of atypia and 6 were suspicious for HGUC. Cytomorphological evaluation of LGUC cases revealed singly scattered cells 13 cases (68.42%), high N:C ratio in 18 (94.74%) cases, granular nuclear chromatin in 11 cases (57.89 %) and thickened nuclear membrane was noted in 15 cases (78.95 %).

Conclusions: Diagnosis of LGUC on cytology is challenging due to low cellularity and subtle nuclear findings that overlap with benign reactive cells. Maximum cases were found to be negative for malignancy (34.37 %). Amongst malignant cases, majority were of HGUC (31.25 %) followed by LGUC (19.79 %).

Keywords: Low Grade Urothelial Carcinoma (LGUC), High Grade Urothelial Carcinoma (HGUC), Urine Cytology, Cytomorphology.

***Correspondence to:**

Dr. Vijeta Tomar,
Assistant Professor, Department of Pathology,
S.M.S. Medical College, Jaipur, Rajasthan, India.

Article History:

Received: 16-12-2020, **Revised:** 07-01-2021, **Accepted:** 29-01-2021

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2021.7.1.019	

INTRODUCTION

The most frequent histologic subtype (>90%) is Urothelial carcinoma.[1] It is more common in males (male: female ratio- 3:1). The gross appearance of urothelial carcinoma may be exophytic or endophytic. Microscopically, the invasion to sub epithelial tissues proceeds in two stages: (a) invasion of the lamina propria which is difficult to detect and (b) invasion of the muscle layer, which has great significance because of its influence on therapy and prognosis.[2] Urine cytology is simple, non-invasive and cost effective diagnostic modality.[3] Its role in the detection of high grade urothelial carcinoma (HGUC) is well established with a reported sensitivity of 50% to 85% depending upon the type of urine sample collected.[4] Urine cytology can detect high grade carcinomas as well as carcinoma in-situ, the latter being flat lesion is difficult to diagnose cystoscopically.[5] The utility of urine cytology in diagnosing low-grade urothelial carcinoma (LGUC) remains controversial with low sensitivity of 10% to 43.6% as reported in the literature.[1,6]

The diagnosis of LGUC on urine cytology is difficult as the tumor cells show subtle nuclear changes and resemble normal urothelial cells. Thus, urine cytology is not considered as a good diagnostic modality for the detection of LGUC.

The aim of the present study is to evaluate the specific cytomorphological features of LGUC in fresh voided urine sample to improve its detection rate.

MATERIALS AND METHODS

A total of 96 patients suspected of bladder cancer were evaluated in a tertiary care centre in north India. Of all the suspected cases of bladder carcinoma, 96 cases were selected where urine cytology, ultrasonography, and cystoscopy as well as bladder biopsy were available. Two H & E stained smears (cytocencentrifuged smears) prepared from each of the urine samples. Bladder biopsy was considered as the gold standard for final confirmation of diagnosis.

Cytomorphological evaluation

Two H & E stained smears (cytocencentrifuged smears) were prepared from each of the urine samples. Following cytomorphological features were evaluated for each case: a) Overall cellularity b) Tumor cells architecture c) Chromatin pattern d) Nuclear membrane contour e) Thickened nuclear membrane and f) Nuclear hyperchromasia.

RESULTS

A total of 96 fresh voided urine samples were evaluated. Out of 96 samples, 30 were diagnosed as high-grade urothelial carcinoma, 19 as low-grade urothelial carcinoma, 6 as suspicious for HGUC, 8 of Atypia and 33 were diagnosed as negative for malignancy. (Table 1)

Table 1: Distribution of cases in present study

S.No	Diagnostic Categories	n	Percentage
1.	HGUC	30	31.25 %
2.	LGUC	19	19.79 %
3.	Suspicious for HGUC	6	6.25%
4.	Atypia	8	8.33 %
5.	Negative for malignancy	33	34.37 %
	TOTAL	96	

Table 2. Cytomorphological features among samples diagnosed with LGUC (*n*=19) on urine cytology

	Cytomorphological features	No of cases
a.	**Cellularity**	
	Low	08 (42.11%)
	High	11 (57.89%)
b.	**Tumor cell architecture**	
	Cell groups	03 (15.79%)
	Papillary clusters	03 (15.79%)
	Single cells	13 (68.42%)
c.	**Nuclear cytoplasmic ratio (N:C)**	
	<0.5	01 (5.26%)
	>0.5	18 (94.74%)
d.	**Chromatin pattern**	
	Finely granular	11 (57.89%)
	Coarse	06 (31.58%)
	Clumped	02 (10.53%)
e.	**Thickened nuclear membrane**	
	Yes	15 (78.95%)
	No	04 (21.05%)
f.	**Nuclear hyperchromasia**	
	Present	03 (15.79%)
	Absent	16 (84.21%)

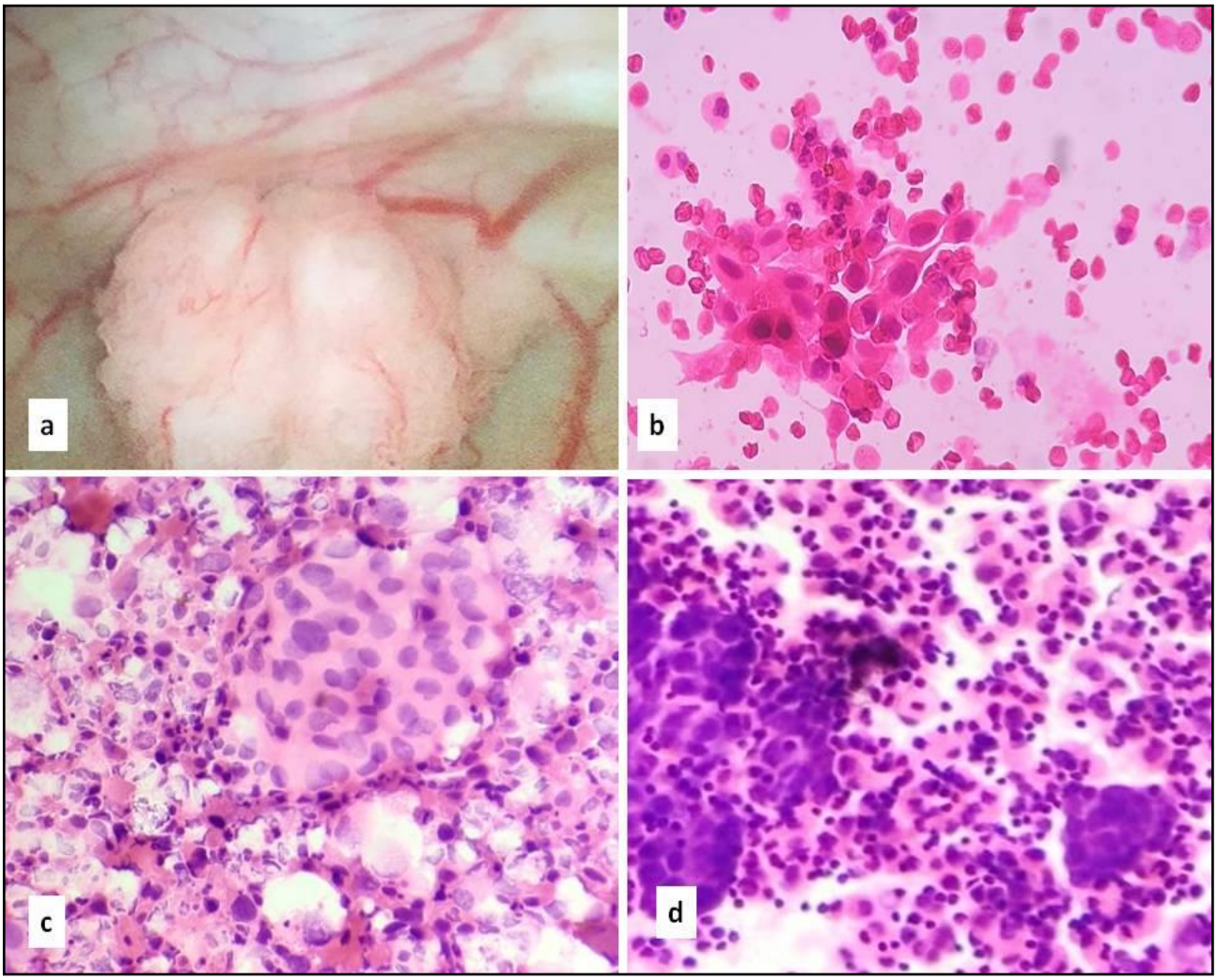

Fig 1. a) Papillary outgrowth seen on cystoscopy. b) Suspicious for HGUC showing cells with high N:C ratio, hyperchromatism. c) LGUC showing high N:C ratio, small cluster, granular chromatin. d) HGUC showing papillary clusters, hyperchromatic cells, high N:C ratio, irregular nuclear outline.

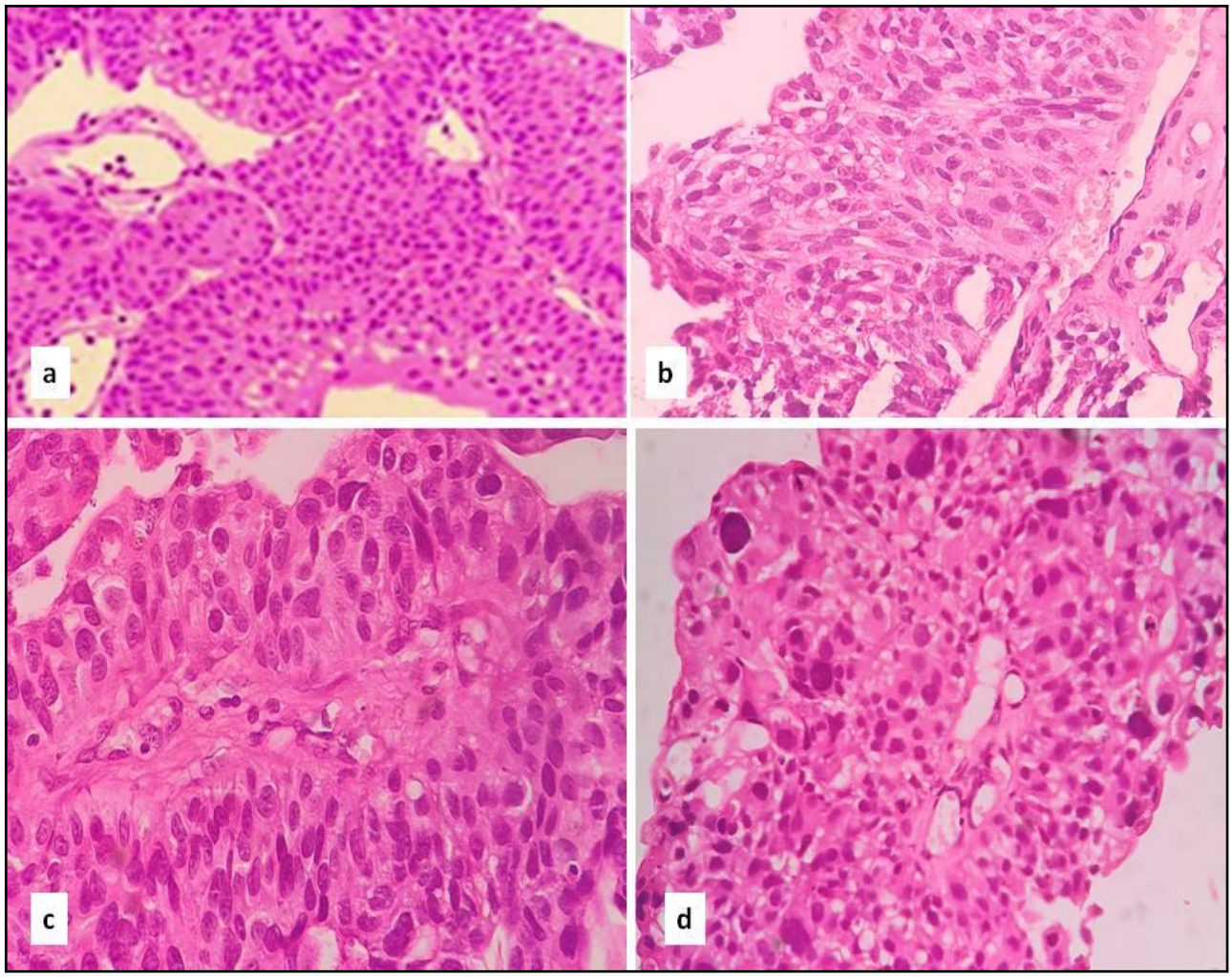

Fig 2. a) & b) LGUC showing papillary architecture, maintained polarity. c) & d) HGUC showing loss of polarity, bizarre cells, brisk mitosis.

In our study 19 cases out of 96 samples were diagnosed as LGUC showing features like the presence of increased cellularity, high N:C ratio, irregular nuclear membrane outline.

Out of 19 samples diagnosed as LGUC on urine cytology, the overall cellularity was low in 8 cases (42.11%). Most of the cases showed singly scattered cells 13 cases (68.42%), whereas only 3 cases (15.79 %) showed the clusters with papillary architecture. The N:C ratio was high in majority cases 18 (94.74%). The nuclear chromatin pattern was mainly showing finely granular nuclear chromatin in 11 cases (57.89 %). Thickened nuclear membrane was noted in 15 cases (78.95 %). However, only a small number of cases (15.79 %) showed nuclear hyperchromasia. [Table 2].

DISCUSSION

In present study maximum cases were negative for malignancy. Amongst malignant cases, were of HGUC comprising 30 cases (31.25 %) followed by LGUC consisting of 19 cases (19.79 %). Suspicious for was found in 6 cases (6.25 %). Atypia was noted in 8 cases (8.33 %). These findings were in concordance with findings of other studies done by Selhi P et al[7], Sushmita et al[8] and Das et al.[9] Studies by Murata et al[10], Goldstein et al[11], Murphy et al[12] and Chung et al[13] have suggested the cytological features which can predict the diagnosis of LGUC in voided urine samples but most of these features overlap with benign reactive conditions.

Murata et al[10] in 2004 reported two cell patterns in LGUC in voided urine samples, “isolated single cell pattern” with low N:C ratio and “cluster pattern” with piled up cellular clusters with high N:C ratio, latter pattern being the predominant pattern. Both patterns showed hyperchromatic nuclei with uneven contour.

In our study, the features that were mainly seen were increased cellularity, high N:C ratio, irregular nuclear membrane outline. Out of 19 samples diagnosed as LGUC on urine cytology, the overall cellularity was low in 8 cases (42.11%), singly scattered cells were seen 13 cases (68.42%), whereas only 3 cases (15.79 %) showed the clusters with papillary architecture. The N:C ratio was high in majority cases 18 (94.74%). The nuclear chromatin pattern was mainly showing finely granular nuclear chromatin in 11 cases (57.89 %) and thickened nuclear membrane was noted in 15 cases (78.95 %).

CONCLUSION

So, it is concluded that the diagnosis of LGUC in voided urine cytology is challenging and low cell yield further makes it difficult to diagnose it on voided urine cytology. Therefore, nuclear atypia, high N:C ratio and papillary fragments should be especially noted. Maximum cases were found to be negative for malignancy. Amongst malignant cases, majority were of HGUC followed by LGUC.

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Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Namrata Aggarwal, Vijeta Tomar, Nitin Negi. Study of Cytomorphological Features of Low-Grade Urothelial Carcinoma And Spectrum of Bladder Tumors Diagnosed on Voided Urine Cytology. Int J Med Res Prof. 2021 Jan; 7(1): 71-74. DOI:10.21276/ijmrp.2021.7.1.019