ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 06 | June - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

KI 67 EXPRESSION IN DIFFERENT HISTOLOGIC VARIANTS OF BLADDER NEOPLASMS: AN INTRIGUING OBSERVATION

Pathology

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ABSTRACT

Bladder neoplasms have diverse categories, both benign and malignant. Ki-67 has increasing expression with increasing grade and stage of cancer. This may serve as an important diagnostic and prognostic marker in Urothelial neoplasms, that may aid in clinical outcome and predict recurrence and progression.

KEYWORDS

Urothelial neoplasm, Ki-67 index, proliferation marker, prognostic marker.

INTRODUCTION

Urinary tract harbors diverse categories of neoplasms ranging from benign to dysplastic as well as invasive malignant processes. Bladder carcinoma is however the most common cancer of urinary tract [1], it being the seventh most common cancer worldwide [2]. Clinically, bladder tumors may be non-muscle invasive (Ta/T1) and muscle-invasive (T2-T4). Cystoscopy and biopsy being the currently available gold standard, there is a need for novel biomarker for early diagnosis, prognostication and effective treatment of Bladder carcinomas.

Ki-67 is a nuclear protein expressed in all stages of cell division [3]. Its predictive role in poor prognosis has been evaluated in different cancers like breast carcinomas [4,5]. However, its role in carcinoma of bladder remains controversial. Ki-67 may also guide in selection of chemoradiotherapy-based multimodal approaches in bladder preservation therapies.

This paper aims to observe the pattern of KI-67 staining in different grades of bladder neoplasm and thereby assess the trend in expression of ki-67 expression in varied neoplasm. This was undertaken in small number of cases in a tertiary care center.

Scenario I: Normal transitional epithelium- In our case, a 57 years old male patient attended a Urosurgery OPD with chronic lower abdominal pain, dysuria that was not resolved even after treatment for Urinary tract infection. CT scan revealed mild wall thickening of bladder that was followed by biopsy. The biopsy however showed **normal urothelial histology**, possibly due to non-representative sampling.

As per our general knowledge of histology, the urothelial lining is 5-7 cell layers thick in contracted bladder and 2-3 in distended bladder with an uppermost umbrella cell lining, intermediate columnar lining and lowermost basal lining. This was the exact picture in this case (Figure 1). **Ki-67** in this case showed **no staining** (Figure 2).

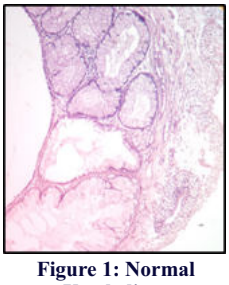

Figure 1: Normal Urothelium

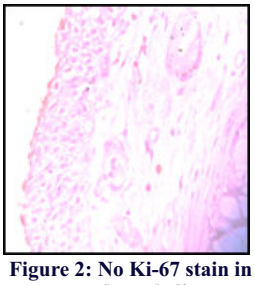

Figure 2: No Ki-67 stain in normal urothelium

Scenario II: Urothelial Papilloma- A 30 years male patient complained of lower abdominal pain and had undergone routine examination of urine which has shown microscopic hematuria (8-10 RBCs/HPF). Conservative management with antibiotics didn't show any improvement. The patient underwent CT imaging that revealed thickening in trigone of bladder. Biopsy was planned for this patient. It revealed papillary architecture with delicate fibrovascular core, lined with normal urothelial lining. A diagnosis of **Urothelial papilloma** was made (Figure 3). **Ki-67** proliferation index was **very low** in this case (Figure 4).

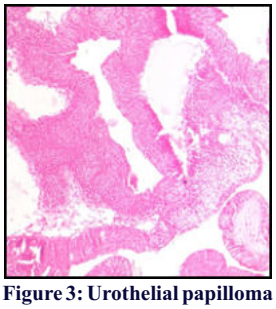

Figure 3: Urothelial papilloma

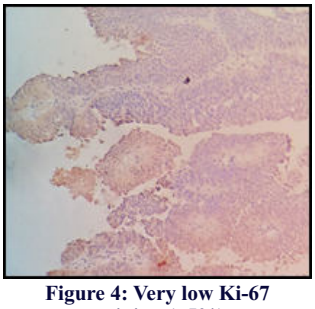

Figure 4: Very low Ki-67 staining (<5%)

Scenario III: Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)- A 60 years old male patient presented with nocturia, dysuria & urgency, not relieved with medication. He had past history of similar complaints that was diagnosed as a case of PUNLMP. Biopsy was planned in this case.

H & E section revealed multiple papillary fronds with thickened urothelial lining and minimal atypia. A diagnosis of **recurrence of Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)** was made (Figure 5). Ki-67 staining showed very low positivity of around 3% (Figure 6).

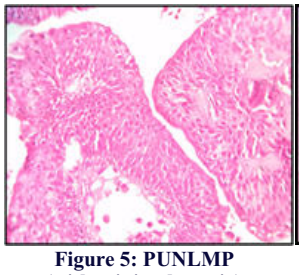

Figure 5: PUNLMP (with minimal atypia)

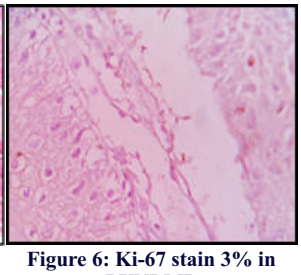

Figure 6: Ki-67 stain 3% in PUNLMP

Scenario IV: Low Grade Non-invasive Papillary Urothelial Carcinoma- A 70 years old male patient attended Urology OPD with painless intermittent hematuria for last 4-5 months. Cystoscopic examination revealed multiple exophytic lesions in bladder.

Biopsy and histopathological examination revealed delicate papillary structures with urothelial lining showing increased thickness, loss of polarity, moderate pleomorphism, increased mitosis. No invasion is seen beyond the basement membrane. A diagnosis of **Low grade Non-invasive Papillary Urothelial Carcinoma** was made (Figure 7). **Ki-67** showed **10%** positivity (Figure 8).

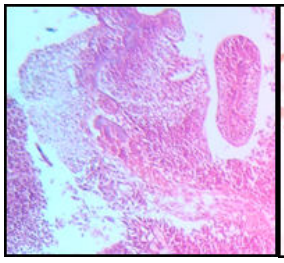

Figure 7: Low grade papillary urothelial carcinoma (non-invasive)

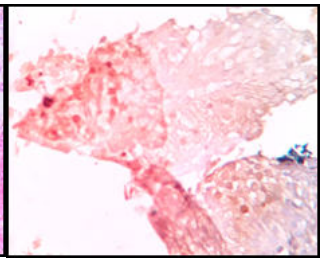

Figure 8: Ki-67 staining showing 10% positivity

Scenario V: Low grade invasive urothelial carcinoma- A 66 years male patient attended OPD with features of UTI but not relieved by medications. Microscopic examination of urine revealed hematuria. MRI study showed exophytic growth in bladder. Cystoscopy and biopsy was scheduled.

Biopsy showed tumor cells with moderate pleomorphism, increased mitosis, loss of polarity infiltrating into lamina propria. Deep muscle was not sampled in biopsy sections examined. A final diagnosis of **Low grade invasive urothelial carcinoma (pT1)** was made (Figure 9). **Ki-67** staining showed **25%** positivity (Figure 10).

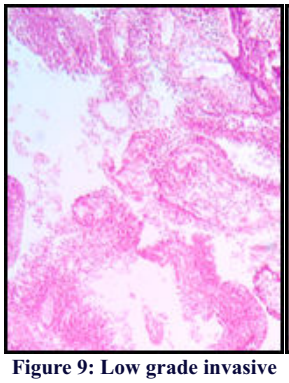

Figure 9: Low grade invasive urothelial carcinoma (pT1)

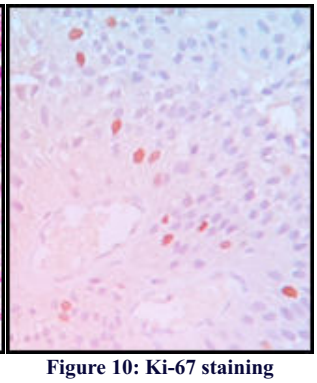

Figure 10: Ki-67 staining shows 25% positivity

Scenario VI: High grade invasive urothelial carcinoma- A 72 years old male patient attended OPD with painless intermittent gross hematuria. He was a known chronic smoker. CT scan imaging delineated exophytic lesions in bladder wall. Cystoscopy and biopsy was done & specimen sent to Department of Pathology for histopathological study.

H & E showed markedly pleomorphic tumor cells with prominent nucleoli at places, focal areas of squamous differentiation infiltrating into lamina propria. Wide areas of necrosis were also seen. Deep muscle was not sampled. A diagnosis of **High grade invasive Urothelial Carcinoma (pT1)** was made (Figure 11). **Ki-67** showed **45%** positivity (Figure 12).

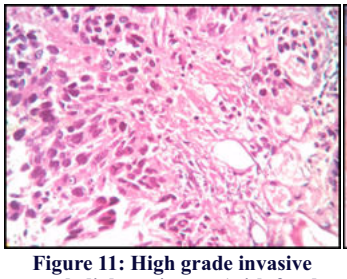

Figure 11: High grade invasive urothelial carcinoma (with focal squamous differentiation)

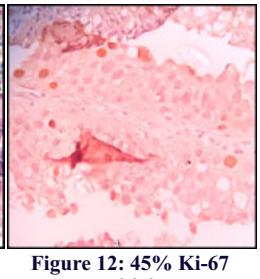

Figure 12: 45% Ki-67 positivity

A 65 years female had similar presentation. Underwent the same diagnostic algorithm to evaluate the case. Biopsy showed markedly pleomorphic tumor cells with prominent nucleoli, increased mitosis & bizarre mitosis infiltrating into deep muscle of bladder. A diagnosis of **High grade invasive urothelial carcinoma (pT2)** was suggested (Figure 13). **Ki-67** staining in this case showed a high positivity of **50%** (Figure 14).

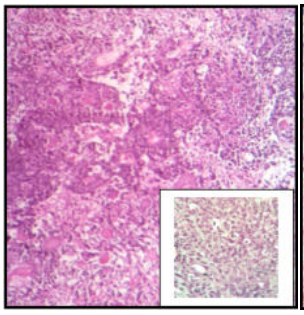

Figure 13: High grade invasive urothelial carcinoma (pT2) [*Inset shows prominent nucleoli*]

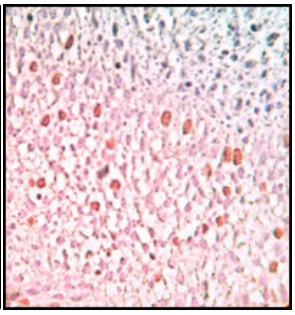

Figure 14: High Ki-67 staining (50%)

DISCUSSION:

As we can see from the above scenarios, bladder neoplasms are of diverse entities. Bladder carcinomas are further staged based on depth of invasion, staging being the single most important prognostic indicator in urothelial carcinomas [6]. Staging is often subjected to inter-observer variations which are critical pathologic issues and are constant source of concern for reporting histopathologists. Grade is also an important histologic discriminant. Thus, proper prognostication of bladder neoplasms may help in risk stratification and identification of cases that will benefit from minimally invasive surgeries.

Previously, there have been contrasting studies on role of Ki-67 in prognostication of Urothelial neoplasms [7]. This study shows the trend in Ki-67 proliferation index with diverse histopathological entities of bladder. The main limitation behind using Ki-67 as a prognostic indicator is lack of any universal cut-off for Ki-67 expression in bladder neoplasm. However, **Ki-67 cutoff of 20%** was the best discriminator for both bladder cancer progression and survival as was seen by Margulis *et al* [8].

Almost all the 7 cases in this study have age >55 years of age, except for Urothelial papilloma that was seen in a relatively younger age group of 30 years. This corroborated with the findings of Tian *et al* [9]. 6 cases were male patients which correspond with the fact that urothelial neoplasms have increased male preponderance [10].

The following **Table 1** describes the summary of the above 7 cases with respect to histologic type & Ki-67 labelling index:

CASE NO.	GENDER	AGE (yrs.)	HISTOLOGIC TYPE	KI-67 INDEX (%)	GRADE OF KI-67 EXPRESSION
1.	Male	57	Normal histology	0	Low grade (<20%)
2.	Male	30	Urothelial papilloma	0	
3.	Male	60	PUNLMP	3	
4.	Male	70	Low grade non-invasive urothelial carcinoma	10	
5.	Male	66	Low grade invasive urothelial carcinoma (pT1)	25	High grade (≥20%)
6.	Male	72	High Grade Invasive Urothelial Carcinoma (pT1)	45	
7.	Female	65	High Grade invasive urothelial carcinoma (pT2)	50	

Thus, we can see that benign bladder neoplasms have very low Ki-67 expression. With malignant neoplasms, there is tendency of increased Ki-67 expression with increasing Grade and stage of tumor. This

corroborated with the findings of Ding *et al* [11] where Ki-67 was associated with tumor grade, stage and other parameters and hence, was a predictor of recurrence and progression. Other studies have also established that Ki-67 proliferative index has an independent validity in high risk superficial bladder tumors or non-muscle invasive tumors who may recur in a short follow-up period [12]. The invaluable role of Ki-67 might also be to differentiate low-grade and high-grade urothelial cell cancers, thereby increasing accuracy of pathological diagnosis and further aiding to clinical outcome [13].

CONCLUSION:

This study showed the trend of Ki-67 expression in different histologic variants of bladder neoplasms. The proliferation index was seen to be higher with increasing grade and stage of tumors. But larger study population with a greater number of sample size is needed to establish any statistical significance amongst these parameters. Considering previous studies where Ki-67 has shown efficacy as both diagnostic and prognostic markers, this may serve as an important immunohistochemical tool in Urothelial neoplasms in the future.

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