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Original Research Article

GATA3 Immunohistochemistry Expression in Differentiating Metastatic Lesions of Bladder from Urothelial Carcinomas of Bladder and its Significance in Different Grades of Urothelial Carcinoma

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Abstract:

Introduction: Urothelial carcinoma is most common type of bladder cancer. Immunohistochemical analysis of urothelial carcinoma is important in the identification of the site of origin of metastatic lesions of unknown primary.

Aim: to explore GATA binding protein 3, a zinc finger transcription factor, immunohistochemistry expression in urothelial carcinomas of the bladder and in metastatic lesions of the bladder.

Methods: It is an observational study where 40 cases of Urothelial carcinoma along with 10 cases of each high Gleason score prostate adenocarcinoma, colon adenocarcinoma, cervix squamous cell carcinoma, and renal cell carcinoma were included. All the cases were histopathologically evaluated and immunohistochemically stained for GATA binding protein 3. Only nuclear positivity was considered as positive. The immunoreactivity score for GATA expression was calculated based on the staining intensity as well as percentage. The statistical analysis was done P value <0.05 was considered significant.

Results: GATA3 expression was seen in 85% of the cases of urothelial carcinoma mostly with moderate to strong positivity whereas none of high gleason score prostate adenocarcinoma, colon adenocarcinoma, cervix squamous cell carcinoma, and renal cell carcinoma were GATA3 positive. GATA3 expression significantly correlated with histological grade and muscle invasion with a weaker or negative expression in high-grade muscle invasive tumor as compared to low-grade. Significantly weaker expression of GATA3 was found in cases with severe nuclear pleomorphism and mitosis >10/10 hpf.

Conclusion: The study concluded that GATA3 immunohistochemistry expression helps in differentiating metastatic lesions of the bladder like high gleason score prostate adenocarcinoma, colon adenocarcinoma, cervix squamous cell carcinoma, and renal cell carcinoma from urothelial carcinomas of the bladder, thereby facilitating the diagnosis, treatment, and management of these cases.

Keywords: GATA3, Carcinoma, Expression, Urothelial.

Introduction

As per the GLOBOCAN 2018, bladder cancer was estimated to have 549,000 new cases and 200,000 deaths per year and was ranked 10th among all cancers in the world; it contributed 3.4% to the total cancer burden worldwide. In India, there were 18,921 new cases and 10,231 deaths with an incidence rate (per 100,000) of 2.4 and 0.7 in men and women respectively and mortality rates (per 100,000) as 1.3 and 0.3 in men and women, respectively; it is ranked 17th in incidence and 19th in mortality[1]. Urothelial carcinoma is most common type of bladder cancer accounts for more than 90% of all bladder cancer. While metastasis accounts for 2% of bladder specimen.[2,3]

Histopathology of Invasive urothelial carcinoma is remarkable for its diversity of morphological manifestations. Some of these patterns are so distinctive that they have been recognized as specific subtypes of urothelial carcinoma like urothelial carcinoma with squamous differentiation, UC with glandular differentiation, nested UC, microcystic UC, micropapillary UC, giant cell UC etc. [4,5]. With wide and varied subtypes of Urothelial carcinoma, it is difficult to diagnose as they morphologically mimic other high grade carcinoma which metastasis to bladder like Prostate adenocarcinoma, Colorectal adenocarcinoma, Renal cell carcinoma, uterine cervix squamous cell carcinoma.

Tumors directly invading the bladder originate in the colorectum, prostate gland, and uterine cervix and rest from bloodborne metastases include the

stomach, skin (melanoma), breast, kidney, and lung [3,6].

Immunohistochemical analysis of urothelial carcinoma is important as the exclusion of secondary involvement of the bladder by carcinoma arising at another site or in the identification of the site of origin of metastatic lesions of unknown primary[8,9]. It is very important to differentiate as the treatment and management vary according to the primary malignancy[8,9].

Many immunohistochemical markers have been studied in the past including p63, cytokeratin 7, cytokeratin 20, uroplakin, placental S100 (S100P), and thrombomodulin, but none of them have proven to be effective in differentiating bladder primary from secondary.[7,8,9]. But studies have shown the expression rate of GATA3 in urothelial carcinoma ranging from 51% to 96% [8-17].

GATA-3 is also known as GATA-binding protein 3 and transacting T-cell-specific transcription factor and it is only recently being recognized as a urothelial-associated immunohistochemical marker.

In this study GATA3 expression in urothelial carcinoma compared with cases of high-grade prostate adenocarcinoma, renal cell carcinoma, colorectal adenocarcinoma, and uterine cervix squamous cell carcinoma.

Material and Methods

It is retrospective observational study which was conducted after the ethical clearance from the ethical committee of institute.

In this study formalin fixed paraffin embedded blocks was divided two groups

Group A- include 40 cases of urothelial carcinoma and Group B- include 40 cases, 10 cases each of high gleason score prostate adenocarcinoma, renal cell carcinoma, colorectal adenocarcinoma and uterine cervix squamous cell carcinoma which can metastasize to bladder.

Inclusion criteria: This study will include formalin fixed paraffin embedded blocks specimen of group A and group B cases received between January 2017 and April 2021 in the Department of Pathology of our institute.

Exclusion criteria: Blocks with inadequate material.

From each formalin fixed paraffin embedded blocks two sections of 3-4-micron thickness using rotatory microtome. One section was stained with hematoxylin and eosin stain for histopathological confirmation of cases and other section for GATA3 immunohistochemical staining.

Immunohistochemical staining: Section for Immunohistochemical staining was taken on 5 - aminopropyltriethoxysilane coated slides and was performed on Leica BOND Max automated slide staining machine with GATA3 Rabbit monoclonal antibody (clone-EP368).

Choriocarcinoma tissue served as positive control, and for negative control, primary antibody was omitted while performing immunohistochemical staining. In every Immunohistochemical staining batch both positive and negative control were included.

Immunohistochemical staining evaluation

Immunohistochemical stained slides were examined under microscope at 400X magnification. Nuclear staining was considered positive. Percentage and intensity of tumor cell stained by GATA3 was scored for each case as following.

- Score 0: No tumor cells stained
- Score 1: 1–10%
- Score 2: 11–50%
- Score 3: 51–80%
- Score 4: 81–100%

The staining intensity of tumor cells labelled by GATA3 was scored as follows:

- Staining Score 0: No tumor cells stained
- Staining Score 1: Weak
- Staining Score 2: Moderate
- Staining Score 3: Strong

For each case GATA3 Immunoreactivity score (IRS) was calculated by multiplying the the number representing the percentage of immunoreactive cells by the number representing staining intensity and the cases were categorized in four groups shown in Table 1.

Statistical Analysis: Categorical variables were expressed as a percentage and were analyzed using the Chi-square test. Continuous variables were expressed as mean and standard deviation and will be analyzed using student T TEST. P-value <0.05 will be considered statistically significant.

Results: A total of 80 cases were studied. The study was divided into two groups. Group A comprising of 40 cases of urothelial carcinoma, Group B comprised 10 cases of Prostate adenocarcinoma, 10 cases of colon adenocarcinoma, 10 cases of Cervix Squamous cell carcinoma, and 10 cases of Renal Cell carcinoma.

GATA3 IHC expression on paraffin embedded tissue sections were categorised as negative, weakly positive, moderately positive and strong positive according to Immunoreactive score. Positive staining was determined as nuclear staining of malignant cell and no cytoplasmic staining was noted.

GATA3 expression was seen in 85% of the cases of Invasive urothelial carcinoma.

Out of 85%, positive cases 47%cases were weak positive while 53% cases were moderate to strong positive. All the cases of high Gleason score Prostate adenocarcinoma; colorectal adenocarcinoma, Cervix squamous cell carcinoma, and Renal cell carcinoma were GATA3 negative. However, there was focal weak staining of GATA3 among 20% cases of squamous cell carcinoma cervix (2/10). The study showed significant positive GATA3 IHC expression in Group A cases (UC) and significant negative GATA3 IHC expression in group B cases (PAC, Colon AC, RCC and Cervix SCC). (P< 0.0001) Among Low-grade lamina propria invading urothelial carcinoma cases, all (10/10) were positive for GATA3 stain with 90% strong positivity and 10 % cases with moderate positivity. In High grade invasive urothelial carcinoma cases (24/30) 80% showed moderate to weak positivity in tumor invading lamina propria and weak positivity in tumor invading muscular is propria. There were 6 cases of high-grade invasive urothelial carcinoma invading muscularis propria that were negative for GATA3 staining.

GATA3 expression also significantly correlated with histological grade (P < 0.001) and muscle invasion (P <0.001) such that the low-grade has strong positivity and moderate-to-weak expression in high-grade invasive tumors with no expression in a few cases.

When GATA3 expression was correlated with nuclear pleomorphism, mitosis, necrosis, and tumor-infiltrating lymphocytes. Weak or negative GATA3 expression was seen with marked nuclear pleomorphism, increased mitotic activity (>10 mitosis/10 high power field), necrosis, and tumor-infiltrating lymphocytes).

Table 1: Grouping of GATA3 along with interpretation Group Immunoreactivity score Interpretation.

Group	Immunoreactivity score	Interpretation
I	0-1	Negative
II	2-4	Weakly positive
III	5-8	Moderately positive
IV	9-12	Strongly positive

Table 2: GATA3 scoring in Urothelial Carcinoma (Group A cases) (n=40)

GATA3 Score	Total	Low Grade Lamina Propria invasion	High Grade Lamina propria invasion	High Grade Muscularis Propria invasion
12	9	9	0	0
9	0	0	0	0
8	0	0	0	0
6	9	1	8	0
4	14	0	5	9
3	0	0	0	0
2	2	0	0	2
1	4	0	0	4
0	2	0	0	2

Table 3: GATA3 scoring in Prostate Adenocarcinoma, Colon Adenocarcinoma, Renal cell carcinoma and Cervix squamous cell carcinoma (Group B cases) (n=40)

GATA 3 score	Total	PAC	Colon AC	RCC	Cervix SCC
12	0	0	0	0	0
9	0	0	0	0	0
8	0	0	0	0	0
6	0	0	0	0	0
4	0	0	0	0	0
3	0	0	0	0	0
2	0	0	0	0	0
1	2	0	0	0	2
0	38	10	10	10	8

None of the high gleason score Prostate adenocarcinoma (PAC), Colon adenocarcinoma (AC), Cervix squamous cell carcinoma (SCC) and Renal cell carcinoma (RCC) were GATA3 positive. However there was focal weak staining of GATA3 among 20% cases of squamous cell carcinoma cervix (2/10).

Table 4: Comparison of GATA3 expression in study Group A and B

Group	GATA3 Expression	Immunore activy score	Group A (n=40)		Group B (n=40)	
			No.	%	N0.	%
I	Negative	0-1	6	15	40	100
II	Weakly positive	2-4	16	40	0	0
III	Moderately positive	5-8	9	22.5	0	0
IV	Strongly positive	9-12	9	22.5	0	0

GATA3 expression was seen in 85% of the cases of urothelial carcinoma All the cases of group B were GATA 3 negative.

Table 5: Statistical analysis of IHC GATA3 expression in Group A and Group B cases

HIC Score	Group A	Group B
Median	4	0
Range	0-12	0-1
Mean±SD	5.7±3.8	0.05±0.22
p value	<0.0001	

The shows significant Positive GATA3 IHC expression in Group A cases(UC) and significant negative GATA3 IHC expression in group B cases (PAC, Colon AC, RCC and Cervix SCC).

Table 6: Intergroup comparison of GATA3 expression with histopathological examination findings of Group a study population

TCC	Total	Group I		Group II		Group III		Group IV		P value
		No.	%	No.	%	No.	%	No.	%	
Grade										
High	30	6	100	16	100	8	89	0	0	**<0.0001**
Low	10	0	0	0	0	1	11	9	100	
Invasion										
Lamina	23	0	0	5	31	9	100	9	100	**<0.0001**
Muscle	17	6	100	11	69	0	0	0	0	
Nuclear pleomorphism										
Mild (1+)	0	0	0	0	0	0	0	0	0	**0.001**
Moderate (2+)	3	0	0	0	0	1	11	2	22	
Severe (3+)	16	0	0	4	25	5	56	7	78	
	21	6	100	12	75	3	33	0	0	
Mitosis										
<5/10 hpf	4	0	0	0	0	2	22	2	22	**0.023**
5-10/10 hpf	20	2	33	6	38	5	56	7	78	
>10/10 hpf	16	4	67	10	63	2	22	0	0	
Necrosis										
Absent	18	2	33	6	38	4	44	6	67	**0.439**
Present	22	4	67	10	63	5	56	3	33	
LVI										
No	34	2	33	14	88	9	100	9	100	**0.001**
Yes	6	4	67	2	13	0	0	0	0	
PNI										
No	37	3	50	16	100	9	100	9	100	**0.0004**
Yes	3	3	50	0	0	0	0	0	0	
TIL										
Absent	10	0	0	2	13	3	33	4	44	0.124
Present	30	6	100	14	88	6	67	5	56	

Table 7: Intergroup GATA3 expression in Group B study population

Prostate Adenocarcinoma Gleason score	Total	Group I		Group II		Group III		Group IV	
		No.	%	No.	%	No.	%	No.	%
5+5=10	3	3	100	0	0	0	0	0	0
5+4=9	6	6	100	0	0	0	0	0	0
Colon Adenocarcinoma	Total	Group I		Group II		Group III		Group IV	
		No.	%	No.	%	No.	%	No.	%

Well differentiated	3	3	100	0	0	0	0	0	0
Moderately Differentiated	4	4	100	0	0	0	0	0	0
Signet Ring Mucinous	2	2	100	0	0	0	0	0	0
	1	1	100	0	0	0	0	0	0
Cervix Squamous cell Carcinoma	Total	Group I		Group II		Group III		Group IV	
		No.	%	No.	%	No.	%	No.	%
Well differentiated	2	2	100	0	0	0	0	0	0
Moderately Differentiated	4	4	100	0	0	0	0	0	0
Poorly Differentiated	2	2	100	0	0	0	0	0	0
Papillary	2	2	100	0	0	0	0	0	0
Renal Cell Carcinoma	Total	Group I		Group II		Group III		Group IV	
		No.	%	No.	%	No.	%	No.	%
Papillary	4	4	100	0	0	0	0	0	0
Clear cell	3	3	100	0	0	0	0	0	0
Chromophobe	3	3	100	0	0	0	0	0	0

Group A (UC) GATA3 IHC Scoring:

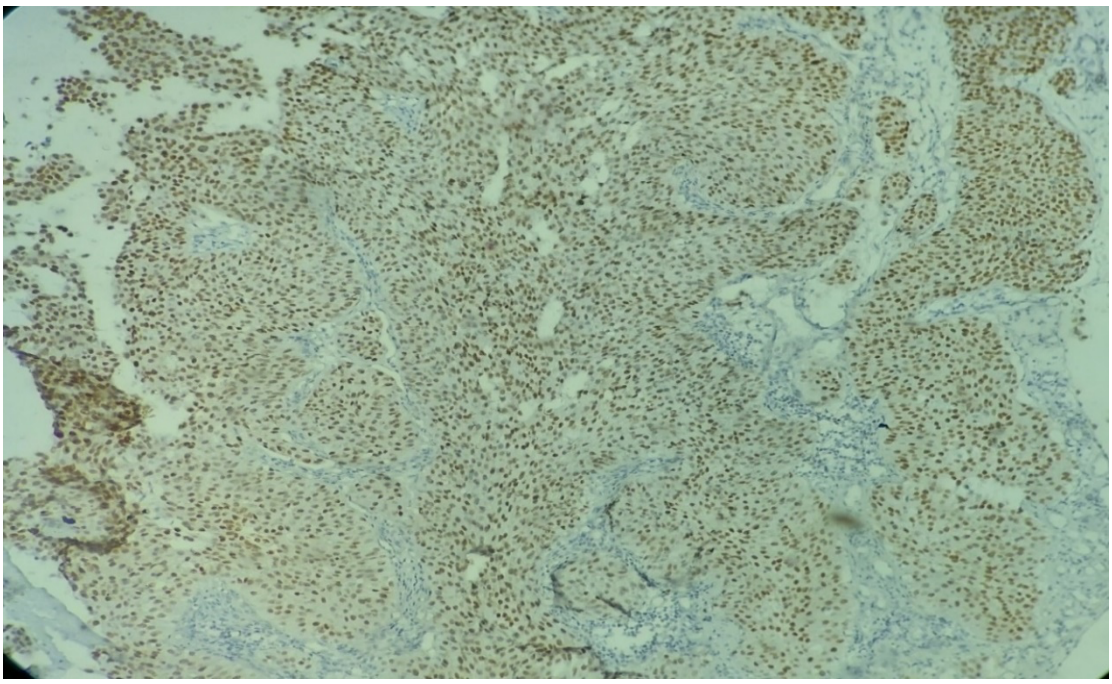

Figure 1: GATA3 IHC Expression in Low-Grade Lamina Propria Invasive Urothelial Carcinoma. GATA3 IHC Score-4X3=12

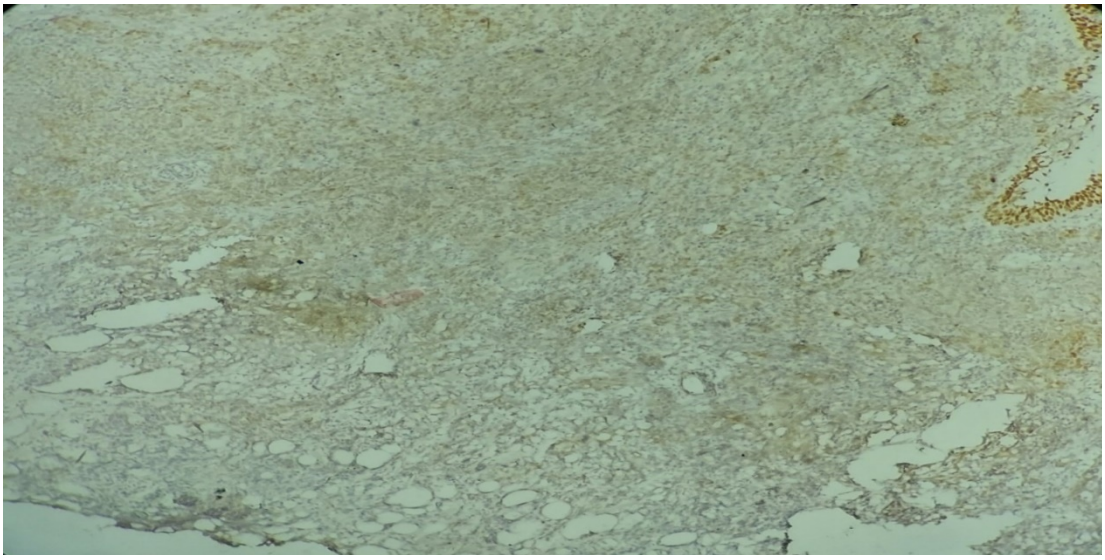

Figure 2: Gata3 IHC Expression in High-Grade Lamina Propria Invasive Urothelial Carcinoma. GATA3 IHC Score-3x2=6

Figure 3: GATA3 IHC Expression in High-Grade Lamina Propria Invasive Urothelial Carcinoma. GATA 3 IHC Score-2X2=4

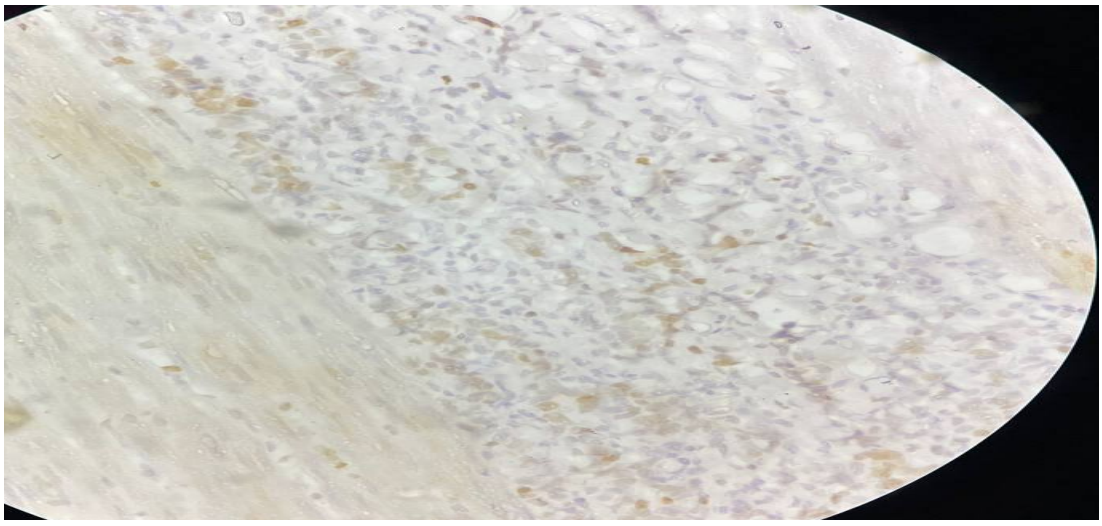

Figure 4: GATA3 Ihc Expression in High-Grade Muscularis Propria Invasive Urothelial Carcinoma. GATA3 IHC Score-2X1=2

Figure 5: GATA3 IHC Expression in High-Grade Muscularis Propria Invasive Urothelial Carcinoma. GATA3 IHC Score-1X1=1

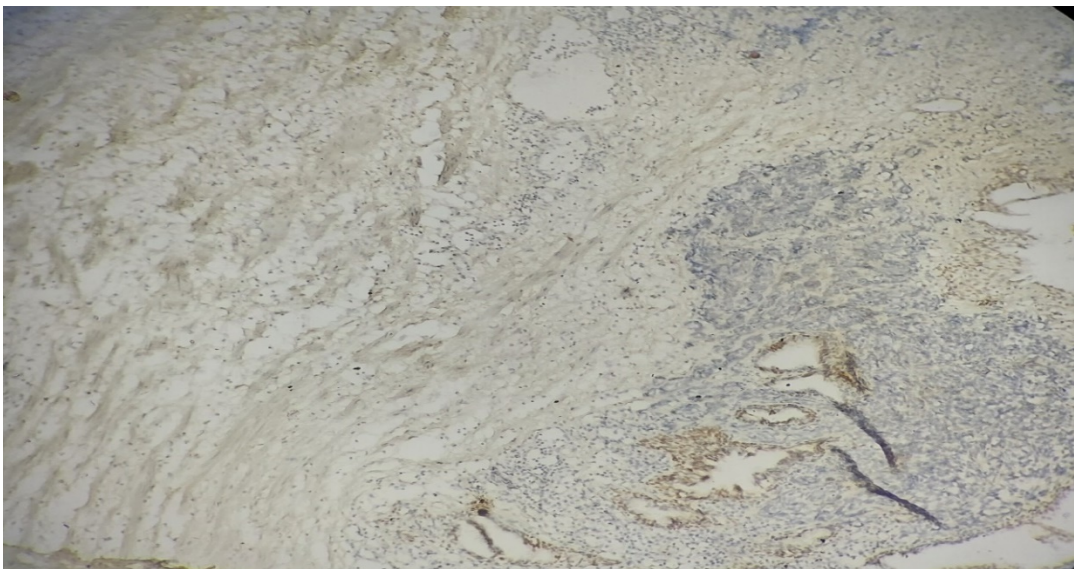

Figure 6: GATA IHC Expression in High-Grade Muscularis Propria Invasive Urothelial Carcinoma. GATA3 IHC Score-0X0=0

Discussion

Bladder cancers 10th most common cancer worldwide. Most common type of bladder cancer is urothelial carcinoma which accounts for more than 90% of all bladder cancer. Secondaries in bladder accounts for 2% of surgically resected specimen. In our study, GATA3 IHC expression in Invasive urothelial carcinoma is statistically significant (P<0.0001). Eighty-five percent of the cases of invasive UC examined were GATA3 positive. This result correlated with studies done by Wang C et al, Chang et al, Naik M et al and Agarwal H et al which showed GATA3 positivity of 87.9, 80%, 79.5%, and 77% in urothelial carcinoma respectively. Out of 85%, positive cases 47%cases were weak positive while 53% were moderate to strong positive. This result is comparable with Agarwal H et al [13] in which 57.75% of GATA3 positive cases showed moderate to strong positivity and Wang C et al [11] study in which 63.7% of GATA3 positive urothelial carcinoma cases showed strong positivity. While most of the positive cases in the study by Abdullah et al [14] and Chang et al [15] were strong and moderate to strong positive respectively. Among Low-grade lamina propria invading urothelial carcinoma cases, all (10/10) were positive for GATA3 stain with 90% strong positivity and 10 % cases with moderate positivity. Agarwal H et al [13] also showed the same finding as 100% moderate to strong positivity in low-grade urothelial carcinoma cases.

In High grade invasive urothelial carcinoma cases (24/30) 80% showed moderate to weak positivity in

tumor invading lamina propria and weak positivity in tumor invading muscularis propria. There were 6 cases (10%) of high-grade invasive urothelial carcinoma invading muscularis propria that were negative for GATA3 staining. The study by Wang et al [11] included only High-grade cases with muscle invasion and found 12% cases GATA 3 negative. GATA3 expression in 2500 Epithelial and nonepithelial tumors was studied by Miettinen M et al(18) and found 100% positivity in low grade and 84% positivity in high-grade urothelial carcinoma. Both the study findings show similarities with our study findings. So far few studies have been done showing the prognostic significance of GATA3 in the urothelial neoplasm. It was first studied by Miyamoto et al [19], and found that loss of GATA3 was associated with high-grade and/or muscle invasion. The same finding was seen in Agarwal H et al [13] study, in which GATA3 expression was significantly correlated with histological grade and muscle invasion with a weaker or negative expression in the high-grade muscle-invasive tumor as compared to low-grade and noninvasive neoplasm [20]. Thus, loss of GATA3 expression in muscle-invasive urothelial tumors in our study is in concordance with the finding of Miyamoto et al [19] and Agarwal H et al[13] study.

Our study also showed a significant statistical association of weak or absent GATA3 expression with other histopathological parameters like marked nuclear pleomorphism ($P < 0.001$), >10 mitosis per 10 high power fields ($P = 0.023$) and presence of LVI (= 0.019).

In study group B none of the high Gleason score Prostate adenocarcinoma, Colon adenocarcinoma, Cervix squamous cell carcinoma and Renal cell carcinoma was GATA3 positives. However, there was focal weak staining of GATA3 among 20% cases of squamous cell carcinoma cervix (2/10). Past studies have shown negative GATA 3 staining in prostate adenocarcinoma, cervix squamous cell carcinoma, renal cell carcinoma, and colon adenocarcinoma.

In the study of Abdullah W.H. et al [14] all the 15 cases of prostate adenocarcinoma were GATA 3 negative. The study by Chang A et al[8] showed negative GATA3 staining in all 38 high-grade prostate adenocarcinoma with weak GATA 3 staining in occasional basal cells of benign prostate glands, in few atrophic glands, and urothelial metaplasia. The study also showed weak nonfocal GATA3 staining in 19% of uterine cervix squamous cell carcinoma.

All the cases of Prostate adenocarcinoma and renal cell carcinoma were GATA3 negative in the study done by Mohammed K.H. et al [16]. The same findings were seen in the study of Agarwal H et al [13] in which none of the clear cell Renal cell carcinoma along with prostate adenocarcinoma was GATA3 positive.

In conclusion with 85% GATA3 Positivity in invasive urothelial carcinoma mostly with moderate to strong positivity and 100% GATA3 negativity in group B cases (PA, Colon AC, RCC, and SCC Cervix). The study concluded that GATA3 immunohistochemistry expression helps in differentiating differentiate metastatic lesions of the bladder from urothelial carcinomas of the bladder.

GATA3 expression was significantly correlated with histological grade and muscle invasion with a weaker or negative expression in the high- grade muscle-invasive tumors as compared to low-grade. Hence GATA3 expression is significant in different grades of urothelial carcinoma. The present study will help in differentiating in group A (UC) and group B (PA, Colon AC, RCC, and SCC Cervix), thereby facilitating the diagnosis, treatment, and management of these cases.

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