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ORIGINAL ARTICLE

# Diagnostic Relevance of GATA 3 Expression in Urinary Bladder Carcinoma of Divergent Differentiation and Other Histological Variants

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**Abstract**
GATA *binding protein 3*, *a zinc finger transcription factor*, has now been demonstrated as a valuable and sensitive marker for conventional urothelial carcinoma with sparse literature related to its expression in various histological variants. It is a prospective study where 74 consecutive cases of bladder carcinoma were included between August 2016 and January 2017 followed by immunohistochemistry to assess GATA 3 expression in conventional as well as different urothelial carcinoma (UC) variants. Overall, 57 of the 74 lesions (77%) demonstrated nuclear staining for GATA 3. GATA 3 expression significantly correlated with histological grade ($P < 0.001$) and muscle invasion ($P = 0.005$). Divergent differentiation was observed in 54% (40/74) of the total cases. The study included 12 different variants of urothelial carcinoma. All or majority of the cases of clear cell (6/6, 100%), glandular (6/8, 75%), and sarcomatoid (4/6, 66.7%) variants expressed GATA 3 in a moderate to strong fashion and belonged to group III or IV. Nested variant, small cell carcinoma, pure squamous cell carcinoma, and squamous component of urothelial carcinoma with squamous differentiation do not show any GATA 3 expression. GATA 3 was expressed more intensely as well as in greater number of tumor cells at lymph node metastatic tumor deposits as compared to the primary tumor. GATA 3 expression was not significantly associated with tumor stage or patients' clinical outcomes. GATA 3 is expressed in majority of variants of UC albeit with variable staining; however, situation is challenging in some variants known to be associated with poor prognosis like nested variant, small cell carcinoma, and squamous cell carcinoma where it is not expressed. Hence, the sensitivity of this determinant is diminished in these variants, which may affect the interpretation of GATA 3 stains at metastatic sites as well as their distinction from secondary bladder involvement, by tumors of non-urothelial origin.

**Keywords** Urothelial carcinoma · GATA 3 · Carcinoma

## Introduction

Bladder cancer (BC) is the ninth most common cancer worldwide with a yearly incidence of approximately 430,000 cases and conventional urothelial carcinoma (UC) accounts for most carcinomas of the urinary tract lining [1]. Neoplastic urothelium has the capacity to demonstrate enormous plasticity and remarkable tendency for divergent differentiation [1]. Hence, UC display a wide range of histomorphological variants with the most common variant being squamous. Some of these variants, such as micropapillary, plasmacytoid, small cell carcinoma, nested, and sarcomatoid, are known to be associated with aggressive biological behavior and poor clinical outcome. The therapeutic approach to these aggressive variants is different from the conventional UC. Also, these variants may mimic some benign lesions of bladder such as cystitis cystica, cystitis glandularis, inverted papilloma, and nephrogenic metaplasia. Thus, their identification is important; however, the histological features of these variants are not specific to UC and can be confused with similar patterns found in many other carcinomas while dealing with tumors of unknown origin at metastatic sites.

Many markers such as p63, CK7, CK20, Uroplakin III, Placental S100, and thrombomodulin have been studied

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in the past, but none of them proved to be both sensitive as well as specific for urothelial carcinoma. In 2007, gene expression analysis revealed a selective expression of GATA in adult urothelium and mammary ductal epithelium [2]. GATA 3 has now been demonstrated as a valuable marker for UC; however, most of the studies so far have focused on conventional UC with very limited literature regarding its expression in different morphological variants [4].

The study of immunohistochemical expression of GATA 3 in different morphological variants of urothelial carcinoma can have diagnostic, therapeutic, and prognostic benefits. With this hypothesis in mind, we conducted this study to evaluate the role of GATA 3 in different histomorphological variants of UC.

## Material and Methods

After obtaining approval from the Institutional ethical committee (IEC), all the histologically proven cases of bladder carcinoma, received in our unit of Department of Pathology, between August 2016 and January 2017 were prospectively included in the study. This study was done in collaboration with Department of Urology. The specimen types included transurethral resection of bladder tissue (TURBT) and radical cystectomy. Previous biopsies of the patient in follow-up were also included wherever possible. The clinical details, including patient demographic characteristics, treatments, and outcomes were retrieved from patient's demographic records. Poorly preserved and inadequate specimens were excluded from the study.

**Histopathological Evaluation** Formalin-fixed paraffin-embedded tissue blocks were used and 3–5-um-thick section from each block was subjected to hematoxylin and eosin staining. All specimens were reviewed by two independent pathologist blinded to the patient identity. The tumors were graded according the World Health Organization/International Society of Urologic Pathology criteria (WHO/ISUP) and staged according to the 2010 American Joint Committee on cancer TNM criteria [5].

**Immunohistochemical Analysis** Three- to 4-um-thick sections from representative paraffin-embedded blocks were taken on 3-aminopropyltriethoxysilane-coated slides and immunohistochemical staining was performed with a monoclonal rabbit antibody raised against human GATA 3 (Clone no. EPR16651, 1:300 dilution, Abcam). Human neuroblastoma tissue was taken as positive control. As a negative control, primary antibody was omitted during staining procedure. Both positive and negative controls were used in each batch of immunohistochemical staining. The slides were examined at × 400 and only nuclear staining was considered as positive. Two independent pathologists performed the immunohistochemical analysis in a blinded manner. The discrepant cases were discussed and finalized by mutual consent. Immuno-reactivity scores for GATA 3 expression were calculated by multiplying the number representing the percentage of immunoreactive cells (0–0%; 1–1 to 10%; 2–11 to 50%; 3–51 to 80%; 4–81 to 100%) by the number representing the staining intensity (0 absent, 1 weak, 2 moderate, and 3 strong).

On the basis of the immunoreactivity score, the patients were categorized in four groups:

Group 1—negative (0–1 score).
Group 2 – weakly positive (2–4 score).
Group 3 – moderately positive (5–8 score).
Group 4 – strongly positive (9–12 score).

Statistical Analysis: The statistical analysis was performed using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The GATA 3 expression in different UC variants was compared with the conventional UC. The values were represented in number (%) and mean ± SD. Chi-square test and Wilcoxon signed rank statistic were used wherever required. $P$ value of $< 0.05$ was considered statistically significant.

## Results

During the period of study, 74 consecutive cases of urothelial carcinoma fulfilling inclusion as well as exclusion criteria were enrolled in the study. The age ranged between 25 and 83 years (mean 55.9 years) with male predominance (M:F = 7.2:1). The most common age group was 40–60 years (60.8%) followed by > 60 years (29.7%). Patients younger than 40 years constituted 9.5% of the total cases. Hematuria was the most common presenting sign, present in 95.95% of subjects followed by urinary outflow obstruction (64.86%). Presenting symptom of weight loss (35.14%) and pain (32.43%) was present among approximately one third of patients.

There were 65 TURBT specimens and 9 radical cystectomy specimens. In radical cystectomy patients, previous diagnostic biopsies were present in 5 cases. Three of the patient also had matched primary and metastatic tumor (lymph nodes). Most of these patients had high-grade ($n = 47$) and invasive UC ($n = 59$) that included Ta ($n = 13$), T1 ($n = 20$), T2 ($n = 33$), T3 ($n = 6$), and T4 ($n = 2$).

Overall, 57 of the 74 lesions (77%) demonstrated nuclear staining for GATA 3. GATA 3 expression significantly correlated with histological grade ($P < 0.001$) and muscle invasion ($P = 0.005$). The low-grade tumors had moderate

to strong expression (24/24 cases) as opposed to high-grade and invasive tumor, which had a weak, or no expression (29/47 cases). The low-grade tumor remained to be moderately to strongly positive for GATA 3 irrespective of their invasion status.

Divergent differentiation was observed in 54% (40/74) of the total cases. This study includes 12 different types of variant of urothelial carcinoma apart from the classical urothelial carcinoma. These morphologic types included 35 cases of conventional urothelial carcinoma, 6 with clear cell differentiation, 8 with glandular differentiation, 6 with sarcomatoid differentiation, 7 with squamous cell differentiation, 3 pure squamous cell carcinoma, 3 plasmacytoid carcinoma, 2 signet ring cell adenocarcinoma, and one case each of inverted, micropapillary, giant, nested, and small cell variants. Table 1 shows the clinical and pathological details of these patients. Table 2 shows comprehensive immunohistochemical results of GATA 3 expression in various morphological variants of urothelial carcinoma.

**Table 1** Clinical and pathologic features of bladder urothelial carcinoma and its variants

| Histological variants | No of cases | Age range/ age in yrs | Gender | | Stage | | | | | Clinical outcome | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Male | Female | Ta | T1 | T2 | T3 | T4 | Alive | Dead |
| Urothelial carcinoma | 35 | 25–83 | 34 | 1 | 9 | 8 | 12 | 5 | 1 | 32 | 3 |
| Clear cell carcinoma | 06 | 45–70 | 2 | 4 | 1 | 2 | 3 | 0 | 0 | 06 | 0 |
| Glandular differentiation | 08 | 50–70 | 8 | 0 | 0 | 2 | 6 | 0 | 0 | 08 | 0 |
| Inverted carcinoma | 01 | 61 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 01 | 0 |
| Giant cell | 01 | 60 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 01 | 0 |
| Micropapillary carcinoma | 01 | 53 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 01 | 0 |
| Nested | 01 | 60 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 01 | 0 |
| Small cell carcinoma | 01 | 65 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 01 | 0 |
| Plasmacytoid | 03 | 65–70 | 3 | 0 | 0 | 1 | 2 | 0 | 0 | 01 | 2 |
| Sarcomatoid | 06 | 52–65 | 6 | 0 | 2 | 1 | 3 | 0 | 0 | 05 | 1 |
| With squamous differentiation | 07 | 32–60 | 6 | 1 | 1 | 1 | 5 | 0 | 0 | 07 | 0 |
| Pure squamous cell carcinoma | 03 | 35–46 | 1 | 2 | 0 | 0 | 2 | 1 | 0 | 03 | 0 |
| Signet ring cell adenocarcinoma | 02 | 65–75 | 2 | 1 | 0 | 1 | 1 | 0 | 0 | 01 | 1 |

**Table 2** GATA 3 immunohistochemical results of urothelial carcinoma variant and conventional urothelial carcinoma

| Differentiation/variants | Total ($n=74$) | Group I ($n=17$) {Negative} | | Group II ($n=15$) {Weakly positive} | | Group III ($n=18$) (Moderately positive} | | Group IV ($n=24$) {Strongly positive} | |
|---|---|---|---|---|---|---|---|---|---|
| | | No | % | No | % | No | % | No | % |
| Clear cell | 6 | 0 | 0.00 | 2 | 13.33 | 0 | 0.00 | 4 | 16.67 |
| Glandular | 8 | 2 | 11.76 | 0 | 0.00 | 4 | 22.22 | 2 | 8.33 |
| Inverted pattern | 1 | 0 | 0.00 | 0 | 0.00 | 1 | 5.56 | 0 | 0.00 |
| Micropapillary | 1 | 0 | 0.00 | 1 | 6.67 | 0 | 0.00 | 0 | 0.00 |
| Nested pattern | 1 | 1 | 5.88 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Plasmacytoid | 3 | 1 | 5.88 | 1 | 6.67 | 1 | 5.56 | 0 | 0.00 |
| Sarcomatoid | 6 | 2 | 11.76 | 1 | 6.67 | 2 | 11.11 | 1 | 4.17 |
| Giant cell | 1 | 0 | 0.00 | 1 | 6.67 | 0 | 0.00 | 0 | 0.00 |
| Signet ring cell | 2 | 0 | 0.00 | 1 | 6.67 | 1 | 5.56 | 0 | 0.00 |
| Small cell carcinoma variant | 1 | 1 | 5.88 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Pure Squamous cell carcinoma | 3 | 3 | 17.64 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| With squamous differentiation | 4 | 3 | 17.64 | 4 (Squamous component was negative) | 0.00 | 0 | 0.00 | 1 | 4.16 |
| Conventional UC | 35 | 4 | 23.53 | 6 | 40.00 | 9 | 50.00 | 16 | 66.67 |

When the expression of GATA 3 was studied in these histological variant of urothelial carcinoma, it was seen that nested variant, small cell carcinoma, pure squamous cell carcinoma, and squamous component of urothelial carcinoma with squamous differentiation do not show any GATA 3 expression (group I) (Fig. 1). However, micro papillary and giant cell variants were weakly positive (Fig. 2).

All or majority of the cases of clear cell (6/6), glandular (6/8), and sarcomatoid (4/6) variants expressed GATA 3 in a moderate to strong fashion and belong to group III or IV (Fig. 3). Both the cases of signet ring cell carcinoma were also positive with one case each in group II (weak positivity) and group III (moderate positivity) (Fig. 2). Similarly, 2 of 3 cases of plasmacytoid variant showed GATA 3 expression; however, it was either weakly or moderately expressed.

The study also includes 3 cases (1 each of squamous cell carcinoma, micropapillary variant, and conventional urothelial carcinoma) where lymph node metastatic deposits were also studied for GATA 3 expression and the results were concordant with the primary site in terms of presence or absence of GATA 3 expression. Although, interestingly, the GATA 3 was expressed more intensely as well as in greater number of tumor cells in two positive cases (micropapillary and conventional urothelial carcinoma) as compared to the primary tumor.

There were 7 patients who succumbed to disease and majority of them (6/7) were either negative or expressed GATA 3 weakly ($p < 0.05$). Similar feature was seen in variants (4 cases) as well, such that all patients who expired had no or weak positivity for GATA 3.

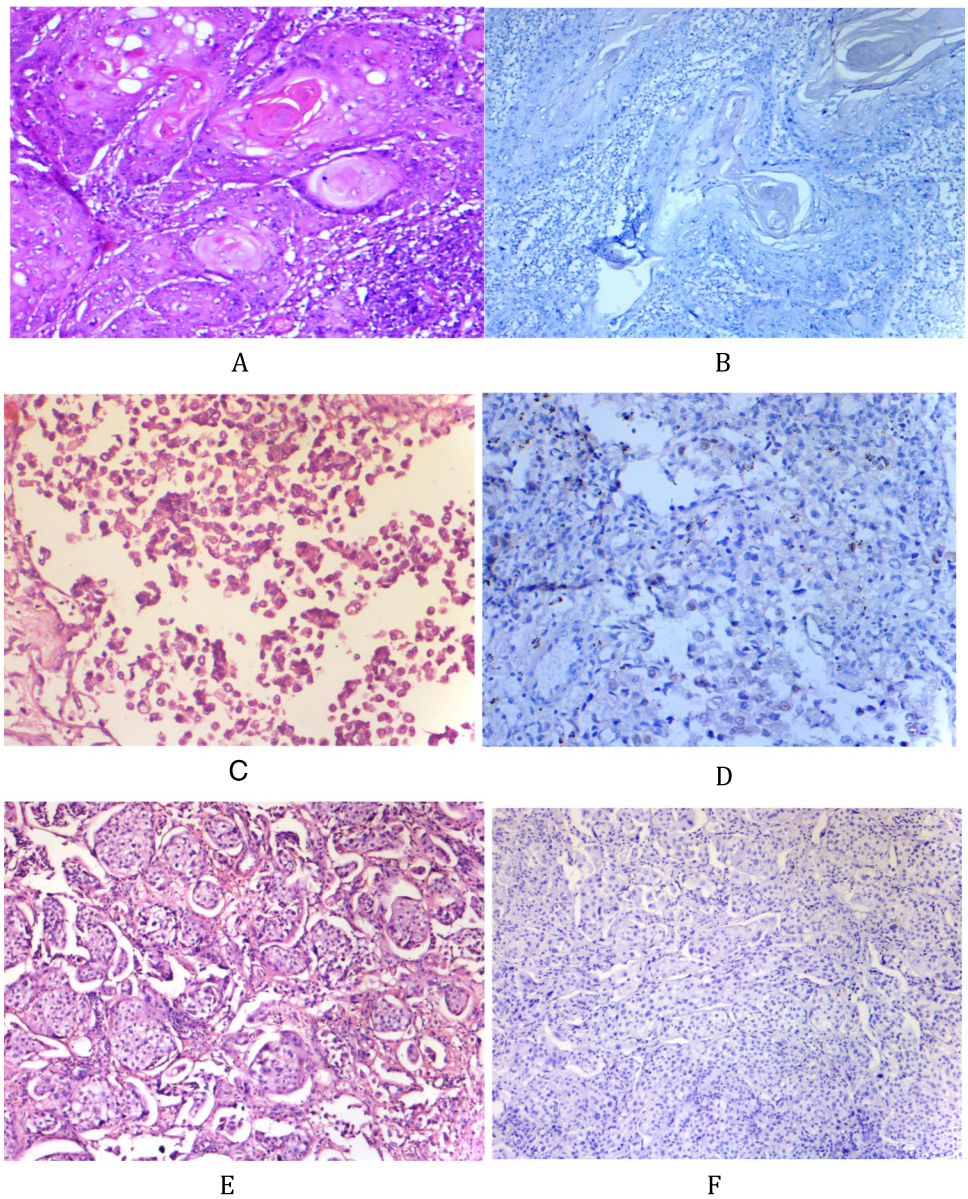


**Fig. 1** Hematoxylin and eosin as well as GATA 3 expression microphotographs in morphological variants of urothelial carcinoma with absence of GATA 3 expression (**A**–**B** squamous cell carcinoma; **C**–**D** plasmacytoid variant; and **E**–**F** nested variant) at × 200

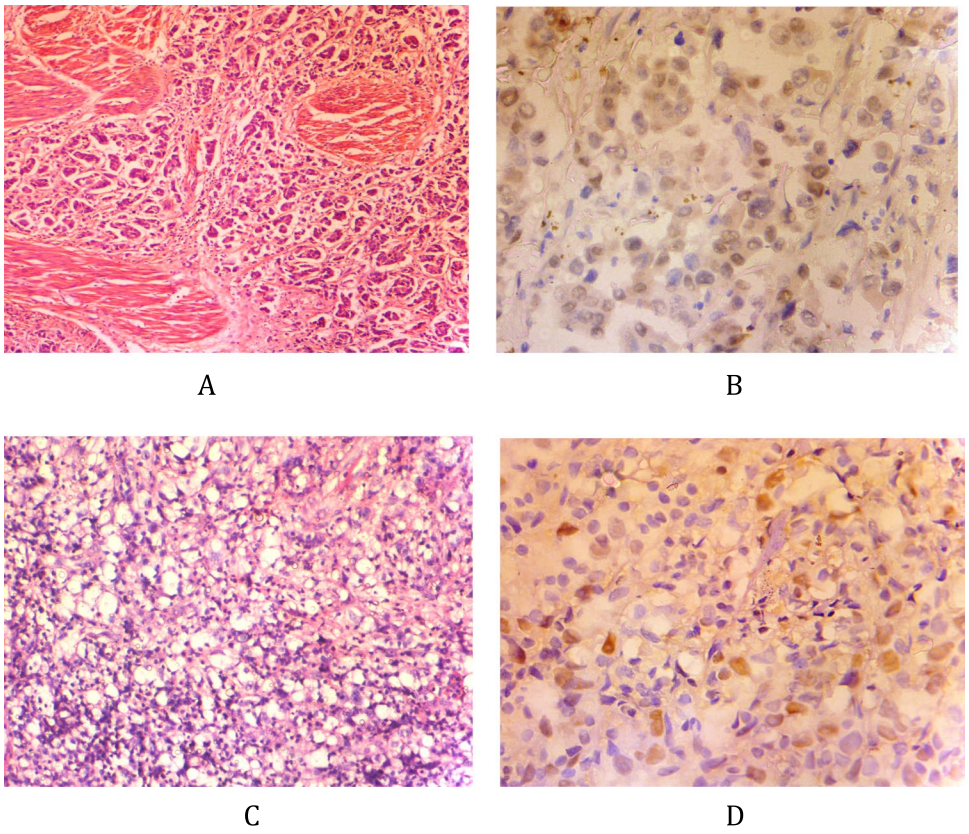


**Fig. 2** Hematoxylin and eosin as well as GATA 3 expression microphotographs in morphological variants of urothelial carcinoma with weak (group II) immunoreactivity to GATA 3 expression (**A**–**B** micropapillary variant and **C**–**D** signet ring cell carcinoma) at × 200

## Discussion

In 2007, Higgins et al. were the first to investigate the expression of GATA 3 as marker for transitional epithelium and UC and suggested it to be highly specific for UC [2]. Since then, few researchers investigated the utility of GATA 3 immunohistochemical expression in various tumors including urothelial carcinoma and concluded that it is a sensitive marker for breast carcinoma and UC [6–8]. Our study published in 2019 also suggested GATA 3 as a sensitive and specific marker for urothelial carcinoma, which can be effectively used to exclude other genitourinary malignancies, prostatic adenocarcinoma, and renal cell carcinoma, at metastatic site. We also demonstrated that the marker could also be effectively used in predicting the probable grade and invasion in biopsy material with poor morphological characteristics, thereby helping in appropriate management in such cases [9].

Morphology of invasive high-grade urothelial carcinoma is not always specific and may morphologically mimic other high-grade metastatic tumors, like prostatic carcinoma, renal cell carcinoma, and squamous cell carcinoma [10, 11]. Also, UC has a remarkable tendency for divergent differentiation, leading to a variety of histological variant which when metastasized can further complicate the situation. It is of utmost importance to recognize these variants as they not only exhibit variable biological behavior but aggressive variants, like plasmacytoid, micro papillary, small cell carcinoma, and sarcomatoid, may benefit from novel therapeutic approaches that differ from those used for convention UC [12].

Great majority of the studies assessing GATA 3 expression in UC were performed on conventional UC with only few studies that had focused on histologic tumor variants with none from India. Liang et al. [3], Verduin et al. [4], and Paner et al. [13] had been the main contributors in this aspect who had studied GATA 3 expression in 6–9 different variants of UC. Ours is the first study from India documenting GATA 3 expression in as many as 12 different variants of UC.

Urothelial carcinomas display a wide range of histomorphological variants with the most common variant being squamous differentiation, with a reported incidence of 20–40% [14]. Divergent squamous differentiation possibly worsen prognosis but pure squamous cell carcinoma bladder is clearly an aggressive lesion. In the present study, we found that 71.4% of urothelial carcinoma with squamous differentiation expressed GATA 3 while all the pure squamous cell carcinoma was negative. Interestingly, the squamous component in the UC with squamous differentiation was also devoid of GATA 3 protein expression. Our results are in accordance with Paner et al. and Gulmann et al. However,

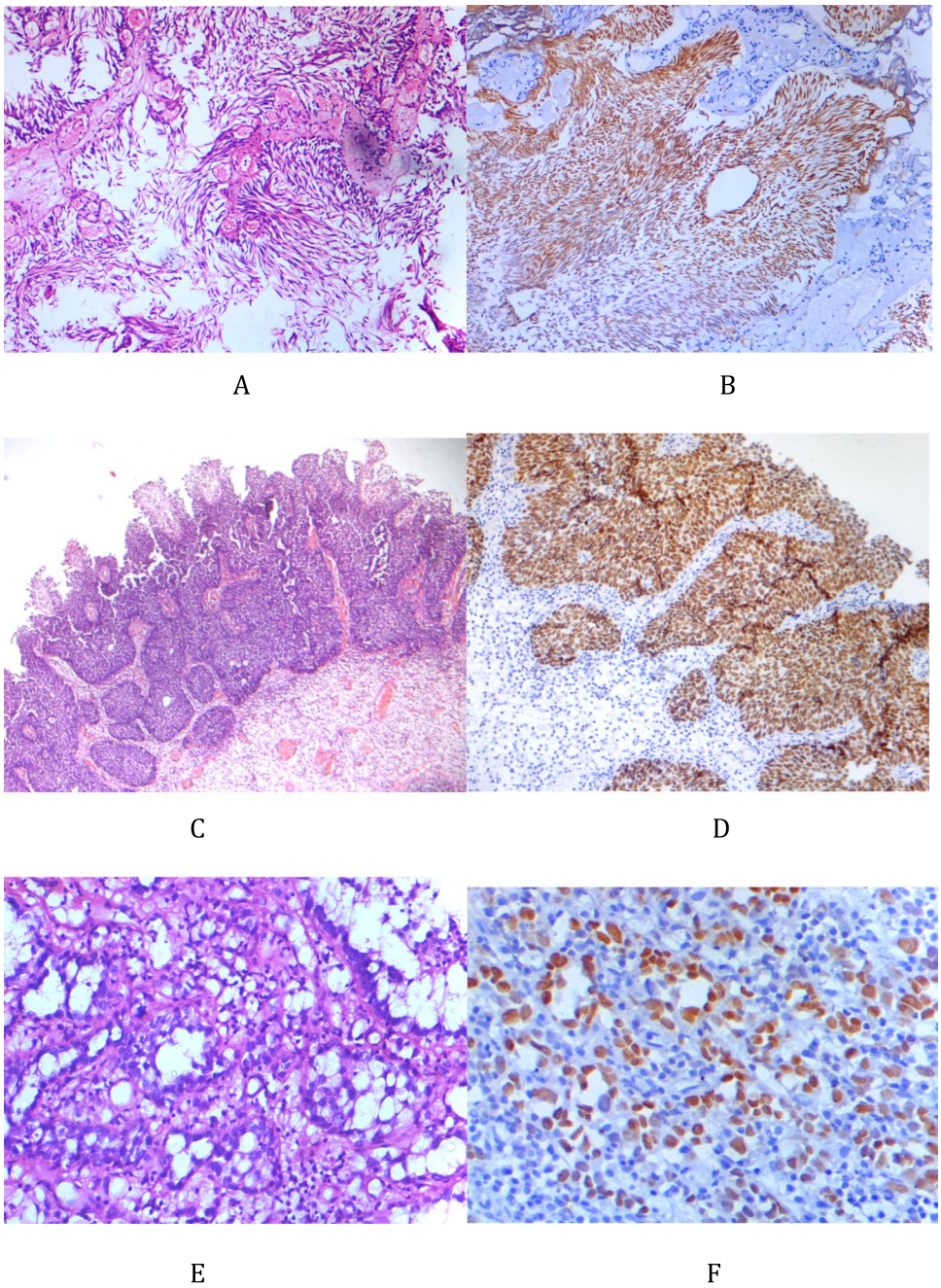


**Fig. 3** Hematoxylin and eosin as well as GATA 3 expression microphotographs in morphological variants of urothelial carcinoma with moderate (group III) to strong (group IV) immuno-reactivity to GATA 3 expression (**A**–**B** sarcomatoid variant; **C**–**D** inverted variant; and **E**–**F** glandular variant) at × 200

few prior studies have documented focal immunoreactivity in pure squamous cell carcinoma [3, 4]. This suggests that the utility of GATA 3 is limited in differentiating UC with squamous differentiation from squamous cell carcinoma of other sites.

Our results show that GATA 3 plays a valuable role in identifying the urothelial origin in clear cell urothelial carcinoma. Clear cell UC is usually diagnosed at higher stage suggesting an aggressive biological behavior. Clear cell morphology is not limited to urinary bladder and can be encountered in tumors from the ovary, kidney, lung, and other organs. All our cases of clear cell UC expressed GATA 3 with 66.7% of them in-group IV displaying strong expression. GATA 3 expression has not been studied extensively in clear cell urothelial carcinomas. We could find only one study by Paner et al. [13], which also had 6 cases of clear cell UC and demonstrated GATA 3 expression in all the cases. Hence, our study along with Paner et al. suggests that if clear cell features are observed at metastatic site, immunohistochemical analysis for GATA 3 expression will help in diagnostic work up for primary origin.

Adenocarcinoma in bladder can represent a pure primary tumor or divergent component in mixed UC. There are limited studies on evaluation of GATA 3 expression in pure primary adenocarcinoma with contradiction [15, 16]. Rao et al. demonstrated that pure primary adenocarcinoma in urinary bladder cases lacked GATA 3 expression while only one of 11 cases of UC with glandular differentiation was positive [15]. Contrary to this, Ellis et al. showed GATA 3 labeling approximately 20% of the cases of pure adenocarcinoma bladder, with a higher percentage in those comprising signet ring cell [16]. Two to 3 years later, studies by Paneret al. and Verduin et al. documented GATA 3 expression in 50% and 44% cases of UC with glandular differentiation, respectively [4, 13]. Our study does not have any case of pure adenocarcinoma bladder; however, two cases of signet ring cell carcinoma and 8 cases of UC with glandular differentiation were included. The results have been more encouraging as compared to past studies, suggesting GATA 3 positivity as a common finding in glandular variant (6/8 cases, 75%) and signet ring cell carcinoma (2/2 cases; 100%).

GATA 3 may also be a useful marker in establishing the urothelial origin in cases of inverted, micro papillary, and giant cell variants as all our cases showed GATA 3 expression; however, there was only single case in each category making these findings statistically insignificant. Similarly, there was one case each of small cell carcinoma and nested variant, both of which were negative for GATA 3.

In our study, GATA 3 expression was present in 2 of 3 plasmacytoid UC. Except for breast lobular carcinoma, non-urothelial neoplasm with plasmacytoid features is usually negative for GATA 3 [3]. Thus, GATA 3 can be a valuable addition to immunohistochemical panel to facilitate the differential diagnosis of neoplasm with plasmacytoid morphology.

An interesting finding in our study was higher expression of GATA 3 in UC sarcomatoid differentiation. We encountered GATA 3 positivity in 66.7% of these cases with variable intensity. Majority of the prior studies have document lower GATA 3 positivity in this variant [3, 6, 13]. A recent study by Verdiun et al. found similar findings in comparison with ours [5], where 8 of 12 cases displayed GATA 3 labeling.

There were three cases where GATA 3 was also analyzed in the primary matched metastatic site (lymph nodes) with concordant results in term of positive expression; however, surprisingly, the GATA 3 expression was present in greater number and with higher intensity in these metastatic tumor deposits. This further suggests that GATA 3 can be a valuable addition to the immunohistochemical panel for tumor of unknown primary origin.

There are several positive aspects of our study: adequate representation of tumor cells by analysis of GATA 3 in full faced section rather than tissue microarray as done in majority of previous studies, inclusion of a wide range of variants as well proper representation of all stages and grade of urothelial carcinoma. We have our fair share of limitations as well most importantly, lesser number of cases in certain variants limiting the statistical power and absence of certain subtypes like microcystic carcinoma, lymphoepithelioma like carcinoma, and pure adenocarcinoma.

In summary, our result suggests that GATA 3 is a sensitive marker for urothelial carcinoma with higher expression in low-grade and non-invasive UC as compared to high-grade invasive tumors. It is expressed in majority of variants of UC albeit with variable staining; however, situation is challenging in some variants known to be associated with poor prognosis like nested variant, small cell carcinoma, and squamous cell carcinoma where it is not expressed. We also found that GATA 3 has a concordant or even higher expression at metastatic sites as compared to primary tumor. Since GATA 3 has a range of sensitivity as a marker for bladder carcinoma with variant morphologic features, hence, proper knowledge of its expression and judicious use can make this protein valuable for identification of urothelial origin at metastatic site; however, additional immunostains may be required in certain situations for ultimate diagnostic recognition.

**Author Contribution** All authors have appropriate contribution to the manuscript as stated in the table as follows. Contribution details (to be ticked marked as applicable):

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Concepts | Y | | Y | | | | | |
| Design | Y | | Y | | | | | |
| Definition of intellectual content | Y | Y | Y | | | | | |
| Literature search | Y | | Y | | | | | |
| Clinical studies | | | | | Y | Y | Y | Y |
| Experimental studies | Y | Y | Y | | | | | |
| Data acquisition | Y | | Y | | | | | |
| Data analysis | Y | Y | Y | | | | | |
| Statistical analysis | Y | | Y | | | | | |
| Manuscript preparation | Y | Y | Y | Y | Y | Y | Y | Y |
| Manuscript editing | Y | Y | Y | Y | Y | Y | Y | Y |
| Manuscript review | Y | Y | Y | Y | Y | Y | Y | Y |
| Guarantor | Y | Y | Y | Y | Y | Y | Y | Y |

**Data Availability** Data may be made available on request.

## Declarations

**Code availability** Not applicable

**Ethics Approval** Approved by Institutional ethical committee.

**Consent to Participate** Not applicable.

**Conflict of Interest** The authors declare no competing interests.

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