Chronic Diseases Journal

DOI: 10.22122/cdj.v13i3.927 Published by Vesnu Publications

Comparison of the expression GATA3 in urothelial bladder carcinoma and prostate carcinoma in Hamadan City, West of Iran in 2020

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Original Article

Abstract

BACKGROUND: Bladder malignancies are a common type of urological cancer leading to a high rate of mortality and morbidity. Bladder cancer is one of the common cancers in the urinary system, which is the 9th cause of cancer in the world. The prompt diagnosis and treatment would result in lower burden of the disease. In this study, immunohistochemical (IHC) assessment of GATA3 expression in bladder carcinoma and prostate carcinoma was performed.

METHODS: In this observational diagnostic study, 90 bladder and 30 prostate cancer biopsies under surgery in Beheshti Hospital in Hamadan City, west of Iran, from February to July 2020, were assessed, and frequency expression of GATA3 in them was evaluated by IHC assay and was compared between bladder carcinoma and prostate carcinoma according to grade. Finally, the results were analyzed by SPSS software.

RESULTS: GATA3 was negative in all prostate carcinoma samples, and it was positive in all urothelial bladder carcinoma samples. The higher GATA3 expression was significantly related to the lower grade of bladder tumor (P = 0.001).

CONCLUSION: Based on the results obtained, it can be concluded that the expression level of GATA3 in bladder carcinoma reaches 100%.

KEYWORDS: Malignancy; Prostatic Neoplasms; GATA3 Transcription Factor; Iran

Date of submission: 06 Mar. 2025, ***Date of acceptance:*** 11 May 2025

Citation: Sadeghi E, Hossainpour H, Jafari M. **Comparison of the expression GATA3 in urothelial bladder carcinoma and prostate carcinoma in Hamadan City, West of Iran in 2020.** Chron Dis J 2025; 13(3): 165-71.

Introduction

Bladder cancer is one of the common cancers in the urinary system, which is the 9th cause of cancer in the world.[1] 50% to 80% of patients with superficial bladder cancer relapse in a 5-year period, and 20% of them develop in grade, which leads to high mortality and morbidity Most bladder urothelial carcinomas (UCs) occur in patients older than 50 years, but it can also occur in younger people or children. Men more than women and white people are more infected by urothelial bladder carcinoma Prostate adenocarcinoma (PAC) and UC are among the most prevalent cancers affecting men globally. These cancers can develop independently within their respective organs – the prostate and urinary bladder – or occur concurrently as separate tumors involving either organ. In some cases, they may also present as a collision tumor.[5] UC and PAC can exhibit similar histological features, which in certain cases, can present diagnostic

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challenges for pathologists.[6] GATA3 immunohistochemistry (IHC) is a well-established diagnostic tool that assists in this particular challenge, as it has been demonstrated to be a sensitive marker for UC and a putatively specific marker for ruling out PAC. GATA3 belongs to a family of six zinc finger transcription factors and plays a crucial role in regulating cell proliferation, development, and differentiation across various tissues and cell types. Recognized as a key urothelial marker, GATA3 is considered one of the most valuable indicators for the diagnosis of UC.[7]

Prostatic and urothelial markers such as NKX3.1, p63, thrombomodulin (TM), and GATA3 are highly valuable for differentiating PAC from UC. While prostate-specific antigen (PSA) serves as an effective clinical screening tool, it is not recommended for distinguishing high-grade tumors due to its inverse correlation with tumor grade – meaning that as the tumor grade increases, the sensitivity of PSA staining decreases.[8] Accurate differentiation between grades of transitional bladder carcinoma is important, because there is a significant difference in the treatment and follow-up of them, but in many cases, this is not possible just by using histopathological changes.[8,9] Various IHC stains, including cytokeratin staining, were used for the definitive detection of urothelial tumors, as the ck7 and ck20 were positive, but this staining is not specific to these tumors, and it is also positive in gastrointestinal tumors.[9] Besides, when urothelial tumors are not very differentiated, they lose reactivity to ck20. The GATA3 protein binding is a member of GATA family that is a transcription factor.[10] It is a new IHC marker for breast tumors and urothelial tumors.[11] Several studies have indicated that GATA3 functions as a tumor suppressor, playing a key role in preventing the progression and metastasis of urothelial cancer. If GATA3 IHC expression varies between different tumor grades, it could potentially be useful for evaluating biopsy specimens.[12] Most studies on GATA3, primarily centered on breast cancer, have shown that combining GATA3 with another indicator can more accurately predict prognosis than using either marker alone.[13] In this study, we would like to differentiate low-grade tumors from high-grade ones by using IHC to investigate the expression of GATA3 on the surface of tumor cells in patients with different grades of transitional bladder carcinoma in west of Iran.

Methods

In this observational diagnostic study, 120 cystectomy specimens and urinary bladder biopsies received from urology and surgery department and diagnosed as urinary bladder neoplasms in the Department of Pathology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran, including 90 cases of transitional bladder carcinoma and 30 cases of PAC which underwent surgery in Beheshti Hospital, Hamadan City, from February to July 2020, were assessed. The research received approval from the Research Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1396.583). We isolated 90 bladder transitional tumor samples that were diagnosed (30 cases of grade 1, 30 cases of grade 2, and 30 cases of grade 3). The expression of GATA3 was determined by IHC assay. Then, 30 PAC tumor samples were also assessed to evaluate the expression of GATA3 by IHC kit (DAKO, Carpinteria, CA, USA). According to the protocol, following steps for each case were taken respectively: 1) cutting and mounting sections on slides coated with suitable tissue adhesive, 2) de-paraffinizing sections in xylene substitutes, 3) re-hydrating through graded alcohols, 4) washing slides in running tap water, 5) performing antigen retrieval as required, 6) washing slides in de-ionized water, 7) applying peroxidase block to neutralize

endogenous peroxidase activity and leaving it on for 5 minutes, 8) washing in tris-buffered saline (TBS) for 2 × 5 minutes, 9) incubating with protein block for 5 minutes, 10) washing with optimally ready-to-use primary antibody, 11) washing in TBS for 2 × 5 minutes, 12) incubating with post-primary antibody for 30 minutes, 13) washing in TBS for 2 × 5 minutes, 14) incubating with linked-vision polymer for 30 minutes, 15) washing in TBS for 2 × 5 minutes with gentle rocking, 16) developing peroxidase activity with 3,3′-diaminobenzidine (DAB) working solution for 5 minutes, 17) rinsing slides in water, 18) counterstaining with hematoxylin, 19) washing the slides with water for 5 minutes, and 20) dehydrating, clearing, and mounting sections. Finally, after statistical data collection, the results were analyzed by SPSS software (version 16, SPSS Inc., Chicago, IL, USA). The chi-square test (χ^2) was used to evaluate associations between studied variables, and a statistically significance level was considered as P-value < 0.05.

Results

Both hematoxylin and eosin (H&E) and GATA3 staining were provided to compare (Figure 1). Strong, moderate, and relatively weak positive staining of GATA3 was observed in scattered various grades of transitional cell carcinoma (TCC) in parts D, E, and F, respectively. On the other hand, part A that was associated with low malignant potential TCC showed papillary structures that lined by monomorphic urothelial cells.

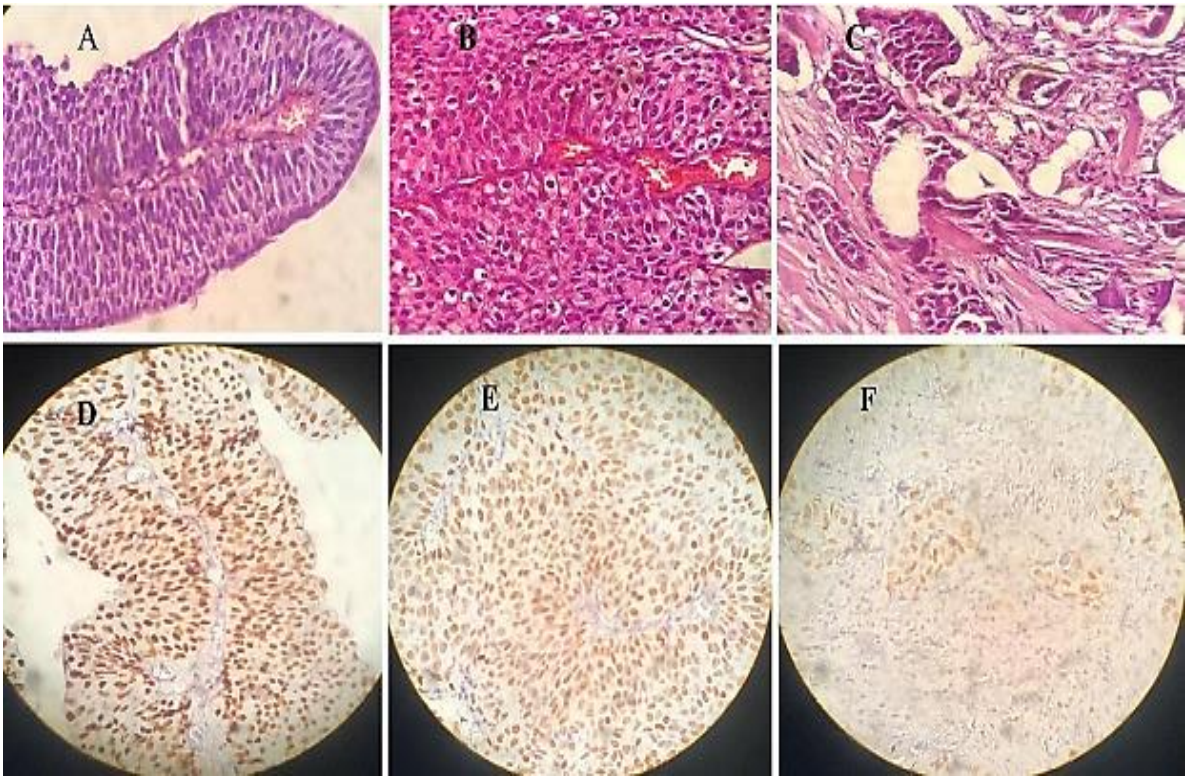

Figure 1. A-C) Associated hematoxylin and eosin (H&E)-staining, transitional cell carcinoma (TCC) grade 1 showing papillary structures (A ×400), TCC grade 2 showing papillary and solid structure (B ×400), TCC grade 3 showing solid sheets and cords (C ×400); D-F) Associated GATA3 staining, TCC grade 1 showing strong positive staining (D ×400), TCC grade 2 showing moderate positive staining (E ×400), TCC grade 3 showing weakly positive staining of GATA3 (F ×400)

Table 1. Frequency of GATA3 stainability intensity distribution according to type and grade

		Intensity				Total
		0	1	2	3	
Sample	TCC1	0 (0)	0 (0)	10 (33.3)	20 (66.7)	30 (100)
	TCC2	0 (0)	2 (6.7)	8 (26.7)	20 (66.7)	30 (100)
	TCC3	0 (0)	14 (46.7)	14 (46.7)	2 (7.6)	30 (100)
	Prostate cancer	30 (100)	0 (0)	0 (0)	0 (0)	30 (100)
Total		30 (25.0)	16 (13.3)	32 (26.7)	42 (35.0)	120 (100)

TCC: Transitional cell carcinoma

Moreover, part B which was associated with low-grade invasive TCC showed papillary and solid structures that lined by polymorphic urothelial cells. Part C that was associated with high-grade invasive TCC showed solid sheets and cords of pleomorphic transitional cells associated with muscular invasion. The frequency distribution of stainable intensity according to type and grade had a significant difference (P = 0.001). In cases with low-grade bladder tumors, stainable intensity was higher, and in PAC, stainable intensity was negative (Table 1).

Distribution of stained cells according to type had a significant difference (P = 0.001), and in cases with low-grade tumor, the rate was higher in this regard, and there was a significant difference between the prostate and bladder carcinoma (Table 2).

Distribution of total scores according to the type of sample had a significant difference (P = 0.001), and in cases with a low-grade tumor, its levels were higher, and there was a significant difference between the prostate and bladder carcinoma samples (Table 3).

Discussion

Bladder cancer is among the most prevalent urological cancers and is a leading cause of cancer-related mortality worldwide.[14] The GATA3 association with bladder cancer characteristics leads to a more accurate marker in determining grading, survival, prognosis, and tumor predicting response rate.[15] Besides, we need to have more specific criteria for deciding on more aggressive treatments. Therefore, in this study, GATA3 expression by IHC in bladder carcinoma was assessed. Overall, according to obtained results, it was concluded that GATA3 expression was negative in all prostate carcinoma samples, whereas it was positive in all bladder carcinoma samples. The GATA3 expression had a significant reverse association with the grade of bladder carcinoma (P = 0.0001). In the study by Liu et al., expression of GATA3 by IHC method in 1110 tumor samples and 110 normal samples was assessed, and in micro-cutting, GATA3 was positive in 86% of UCs and 94% of breast carcinomas, and it was only positive in 2 out of 96 endometrial carcinomas cases, that this point about prostate cancer was consistent with our study. Moreover, in fine-needle aspiration (FNA) samples, GATA3 in 88% of breast carcinomas and 82% of UCs was positive.

Table 2. Frequency of GATA3-stained cells distribution according to type and grade

		Tumor cell GATA3					Total
		0	1	2	3	4	
Sample	TCC1	0 (0)	0 (0)	0 (0)	0 (0)	30 (100)	30 (100)
	TCC2	0 (0)	0 (0)	2 (6.7)	2 (6.7)	26 (86.7)	30 (100)
	TCC3	0 (0)	6 (20.0)	14 (46.7)	4 (13.3)	6 (20.0)	30 (100)
	Prostate cancer	30 (100)	0 (0)	0 (0)	0 (0)	0 (0)	30 (100)
Total		30 (25.0)	6 (5.0)	16 (13.3)	6 (5.0)	62 (51.7)	120 (100)

TCC: Transitional cell carcinoma

Table 3. Frequency of total scores distribution according to type and grade

		Total score				Total
		0	1	2	3	
Sample	TCC1	0 (0)	0 (0)	0 (0)	30 (100)	30 (100)
	TCC2	0 (0)	0 (0)	4 (13.3)	26 (86.7)	30 (100)
	TCC3	2 (6.7)	8 (26.7)	14 (46.7)	6 (20.0)	30 (100)
	Prostate cancer	30 (100)	0 (0)	0 (0)	0 (0)	30 (100)
Total		32 (26.7)	8 (6.7)	18 (15.0)	62 (51.7)	120 (100)

TCC: Transitional cell carcinoma

The study showed that GATA3 was a sensitive and specific marker for the diagnosis of breast carcinoma and UC and should be used for screening of unidentified tumor that suspected breast carcinoma and UC ,[16] which is similar to our research findings. Additionally, GATA3 plays a role in the formation and differentiation of normal tissue, and in regulating cell differentiation and suppressing tumor metastasis.[10] Chang et al. found that GATA3 was positive in 80% of the metastatic UC; however, it was not positive in any of small cell lung cancer (SCLC) and high-grade prostate carcinoma,[17] which is consistent with our research findings that all cases of prostate cancer were negative. Gruver et al. found that GATA3 was positive in 78% of primary metastatic urothelial tumors compared with 23% of SCLCs,[18] and this study showed that it was less specific. Liang et al. studied the expression of GATA3 in various variants of urothelial tumors and concluded that its expression was different in variants of urothelial tumors, and it was useful for evaluating micropapillary and plasmacytoid variants.[19] The observations of our study were similar to Higgins et al.[1] and Doamekpor et al.[20] who exhibited GATA3 positivity in 67% and 70.8% of cases, respectively. No statistically significant correlation was observed in expression of GATA3 with age and sex of the patients. Similar findings were seen in the study conducted by Agarwal et al., where no statistically significant correlation was observed with age and sex of the patients.[21] Miettinen et al. documented GATA3 expression across a range of epithelial and non-epithelial tumors. In breast cancer, ductal and lobular carcinomas demonstrated high GATA3 expression rates, with 92% and 100%, respectively.[22] However, certain tumor types exhibited very low GATA3 expression levels. Neuroendocrine tumors, such as SCLC and Merkel cell carcinoma (MCC), showed no GATA3 expression in any cases.[22] Some carcinomas – including colorectal adenocarcinoma, hepatocellular carcinoma, cholangiocarcinoma, gastric adenocarcinoma, lung adenocarcinoma, and papillary and follicular thyroid carcinoma – exhibit GATA3 expression in less than 10% of cases.[22]

This study has several limitations. Firstly, the small sample size restricted the scope of the analysis. Secondly, potential prognostic differences based on histological subtypes could not be thoroughly examined. Thirdly, a detailed analysis considering patients' age was not possible due to limited available information. In summary, although this study offers valuable insights into the potential prognostic role and stratification utility of GATA3 in urothelial bladder carcinoma, further research is necessary to validate and expand upon these findings. A deeper understanding of the molecular mechanisms involving these markers could potentially lead to improved diagnostic accuracy and development of targeted therapies for this disease.

Conclusion

GATA3 is expressed in all urothelial bladder carcinomas and is an important marker for differentiating malignant bladder tumors from prostate cancers. Its presence is also strongly

linked to improved overall survival in patients with urothelial bladder carcinoma. Furthermore, GATA3 expression shows considerable variation across different histologic subtypes. IHC for GATA3 is especially valuable for distinguishing among various subtypes of urothelial bladder carcinoma and for differentiating low-grade from high-grade tumors.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

The authors thank the Vice Chancellor for Research and Technology in Hamadan University of Medical Sciences for financial support.

Financial support and sponsorship

This study was done with the financial support of Hamadan University of Medical Sciences.

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