https://doi.org/10.15218/zjms.2024.036

Immunohistochemical expression of GATA3 in urothelial carcinoma of urinary bladder

Received: 15/08/2022 Accepted: 03/01/2023

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Abstract

Background and objective: GATA3, an emerging immunohistochemical marker, is a zinc finger transcription factor that is expressed in normal urothelial epithelium and its corresponding neoplasms, and it has been recognized as a reliable urothelial related immunohistochemical marker. This study aimed to detect the frequency of GATA3 expression in urothelial carcinoma of urinary bladder and determine its association with some clinicopathologic parameters.

Methods: Seventy-nine formalin fixed paraffin embedded blocks of urothelial carcinoma cases were randomly selected from a private laboratory in Erbil city during October 2019 to October 2021. In this study, GATA3, a Rabbit monoclonal antibody was applied on urothelial carcinoma cases and its expression was assessed.

Results: GATA3 was expressed in 94.9% of the study cases. It was expressed in all non-invasive and low-grade urothelial carcinoma cases and 97.1% of papillary urothelial carcinoma cases, while it down-expressed in high-grade, invasive and non-papillary urothelial carcinoma cases. A significant association was noted between GATA3 expression and tumor pattern (P = 0.034), while no significant association was noted between GATA3 expression and other clinicopathologic parameters like age, gender, tumor grade, lympho-vascular invasion and tumor stage.

Conclusion: GATA3 is a useful diagnostic immunohistochemical marker for urothelial carcinoma, as this marker was expressed in 94.9% of urothelial carcinoma cases with a significant association with tumor pattern. Further studies are required to evaluate GATA3 expression in association with urothelial cancer progression and metastasis.

Keywords: Urothelial carcinoma; GATA3; Immunohistochemistry.

Introduction

Bladder cancer is the tenth most common cancer worldwide. Consistent rising in its incidence is recorded globally, especially in developed nations.[1, 2] Incidence rate is also rising in Iraq,[3] a survey in Sulaymaniyah, Kurdistan revealed that the bladder cancer is among the top ten major cancers in both sexes within all age groups with an incidence rate of 2.2%.[4] Men are more commonly affected by bladder cancer and among them it ranked as the sixth in most commonly diagnosed cancers and ninth leading cause of cancer fatality.[1]

The major risk for urothelial carcinoma (UC), which constitutes about 90% of bladder cancer cases, is tobacco smoking, followed by exposure to chemical carcinogens at particular occupations.[5] These risk factors may have contributed to male predominance in bladder cancer incidence.[1]

In pathogenesis of UC, two molecular pathways have been identified (FGFR3 and P53 mutations). FGFR3 mutation is mostly observed in papillary non-invasive and low-grade tumors, whereas the p53 mutation is remarkably correlated with

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https://doi.org/10.15218/zjms.2024.036

non-papillary, muscle invasive and higher-grade carcinomas.[6-8]

GATA binding protein 3 is a zinc finger transcription factor, encoded by GATA3 gene located on chromosome 10p14, it has an essential role in regulating the proliferation and differentiation of diverse normal tissues and it is expressed in these tissues and their derived neoplasms.[9-11] Primarily, GATA3 was recognized as a T-cell lineage specific factor, and it has been identified to have a significant role in T-cell development.[12, 13] Furthermore, originally it has been detected by complementary DNA microarray as a marker for transitional epithelium and urothelial carcinoma in 2007 by Higgins et al.[14]

Additionally, it has been reported that GATA3 is likely to becrucialin preventing urothelial tumorigenesis,[15] as when compared to normal urothelial tissues; its expression is reduced in UC.[16] As well, it has been suggested that GATA3 has a preventive role in UC progression, and its decreasing in expression might anticipate progression in non-muscle invasive UC. In addition, GATA3 down-expression was recorded in muscle invasive UC and high-grade UC.[16,17]

Promisingly, modern diagnostic surgical pathology has identified GATA3 as a urothelial-related immunohistochemical marker and recognized it as one of the most reliable urothelial markers. There have been few studies on GATA3 expression in urothelial carcinoma, as well as in its various grades and stages with different results.[9, 11, 18-21]

This study aimed to assess the frequency of GATA3 expression in urothelial carcinoma of urinary bladder by using immunohistochemistry, in addition to investigate its association with some clinicopathologic parameters, such as the age, gender of patients, as well as tumor pattern (papillary and non-papillary), tumor grade, lympho-vascular invasion and tumor stage.

Methods

Study design and setting

Seventy-nine formalin fixed paraffin embedded blocks of transurethral resection of bladder tumor and cystectomy specimens diagnosed as urothelial carcinoma were randomly selected from a private laboratory in Erbil city during October 2019 to October 2021. Two sections were prepared from each block; one was stained with Hematoxylin & Eosin for the purpose of histological analysis while the other was used for immunohistochemical evaluation of GATA3 expression. Normal urothelium was included along with tumor wherever possible.

The microscopical classification & grading of the urothelial carcinoma cases were performed according to the 2016 World Health Organization classification system,[22] and the pathological staging was performed according to the eighth edition of the American Joint Committee on Cancer (AJCC).[23]

Ethical consideration

Ethical approval was obtained from the Ethics Committee of Kurdistan Board for Medical Specialties.

Immunohistochemical method:

Sections with a thickness of four micrometers were cut and mounted on charged slides. After drying at 60 °C for one hour, the slides were deparaffinized and rehydrated at room temperature (20-25 °C). The slides were placed in a xylene bath and after 5 minute incubation put in ethanol for next 3 minutes. Lastly, immersion in distilled water was done for 30 seconds. Epitope retrieval was carried out by using a specific method in 10 mmol/L citrate buffer 1:10 ratio with distilled water. IHC staining was performed using (DakoEnVision FLEX+) system. GATA3 antibody, a rabbit monoclonal antibody (Clone: EP368; catalog no: BSB 3332; 0.5ml concentrated; dilution 1:200) was applied on tissue sections.

The reactivity for GATA3 was considered as positive when nuclear staining was

https://doi.org/10.15218/zjms.2024.036

observed and scoring of GATA3 immunoreactivity was done and reviewed by two expert pathologists. Positive and negative control slides were involved with each run of staining. Negative controls were obtained by omitting the primary antibody and by using N-Universal negative control, normal urothelium was used as positive control for GATA3 expression.

Scoring system:

For scoring of the GATA3 expression, the immunoreactive score (IRS) was used, which multiplies both the percentage of immunoreactive cells and the staining intensity as follows: The percentage of immunoreactive cells was scored as: 0% (0), 1%-10% (+1), 11%-50% (+2), 51%-80% (+3), 81%-100% (+4).

The staining intensity was scored as: Negative (0), weak (+1), Moderate (+2), and Strong (+3). GATA3 IHC scoring results ranged from (0-12),from (0-1): Negative, from (2-4): Weakly positive, from (5-8): Moderately positive, from (9-12): Strongly positive. All three groups which exhibit different positive expressions were regarded as GATA3 positive.[18, 24]

Statistical analysis:

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Chi square test of association was used to compare proportions of two or more groups. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. A *P* value of ≤ 0.05 was considered as statistically significant.

Results

Seventy-nine cases of urothelial carcinoma were included in the study. The patients' age ranged from 40-91 years, the mean age (SD) was 68.1 (10.9) years and the median age was 70 years. The majority of the patients (77.2%) were more than 60 years. There were 61 males and 18 females, i.e. majority of the patients (77.2%) were males as shown in Table 1.

The data for pathologic characteristics of the studied cases are summarized in Table 2.

No significant association was detected between GATA3 expression with age (*P* = 0.613) and gender (*P* = 0.154), but it is evident in Table 3 that the proportions of cases with strongly positive expression were higher among those aged more than 60 years. No significant association was detected between the GATA3 expression with tumor grade (*P* = 0.061), and Lympho-vascular invasion (*P* = 0.337). Although there was no significant association between GATA3 expression with tumor stage (*P* = 0.107), but it appears that 37.5% of cases with Ta (non-invasive UC) and 22.2% of T1 (Lamina propria (LP) invasive UC) had strongly expressed GATA3, as presented in Table 3, Figure 1.

Table 1 Age and gender distribution of the studied cases

	No.	(%)
Age (years)		
≤ 60	18	(22.8)
> 60	61	(77.2)
Mean (SD)	68.1	(10.9)
Gender		
Male	61	(77.2)
Female	18	(22.8)
Total	79	(100.0)

https://doi.org/10.15218/zjms.2024.036

Table 2 Pathologic characteristics of the studied cases

	No.	(%)
Tumor pattern		
Papillary	69	(87.3)
Non-papillary	10	(12.7)
Tumor grade		
Low grade	20	(25.3)
High grade	59	(74.7)
Lymphovascular invasion		
Positive	7	(8.9)
Negative	72	(91.1)
Tumor stage		
Ta	8	(10.1)
T 1	54	(68.4)
T 2	15	(19.0)
T 3	2	(2.5)
GATA3 expression score		
Negative	4	(5.1)
Weakly positive	23	(29.1)
Moderately positive	36	(45.6)
Strongly positive	16	(20.2)
Total	79	(100.0)

GATA3 expression was significantly associated with tumor pattern, (P = 0.034).

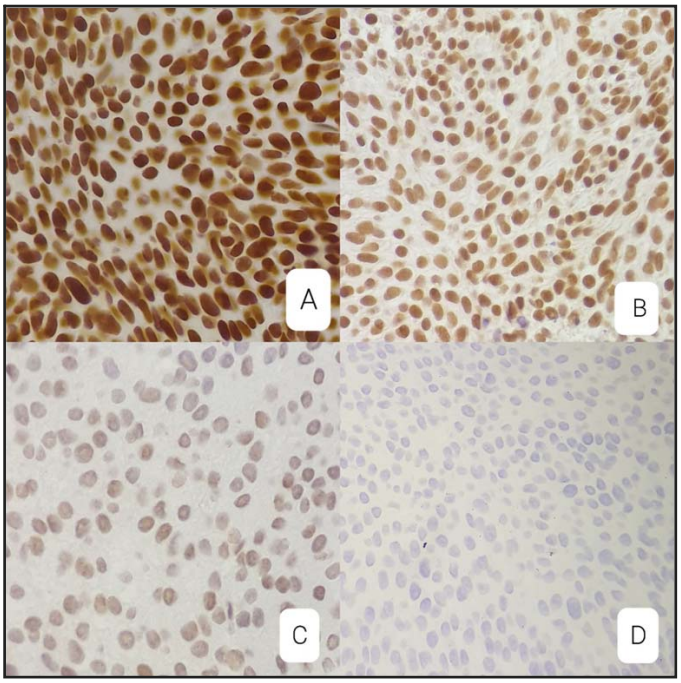

Figure 1 GATA3 immuno-expression. A: Strong intensity GATA3 expression (IHCx400). B: Moderate intensity GATA3 expression (IHCx400). C: Weak intensity GATA3 expression (IHCx400). D: Negative GATA3 expression (IHCx400).

https://doi.org/10.15218/zjms.2024.036

Table 3 The correlation between GATA3 expression and clinicopathologic parameters

		GATA3 expression score				
		Negative	Weakly positive	Moderately positive	Strongly positive	
	N	No. (%)	No. (%)	No. (%)	No. (%)	*P* –Value
Age (years)						
≤ 60 years	18	1 (5.6)	7 (38.9)	8 (44.4)	2 (11.1)	
> 60 years	61	3 (4.9)	16 (26.2)	28 (45.9)	14 (23.0)	0.613*
Gender						
Male	61	4 (6.6)	16 (26.2)	31 (50.8)	10 (16.4)	
Female	18	0 (0.0)	7 (38.9)	5 (27.8)	6 (33.3)	0.154*
Tumor pattern						
Papillary	69	2 (2.9)	18 (26.1)	34 (49.3)	15 (21.7)	
Non-papillary	10	2 (20.0)	5 (50.0)	2 (20.0)	1 (10.0)	0.034*
Tumor grade						
Low grade	20	0 (0.0)	2 (10.0)	13 (65.0)	5 (25.0)	
High grade	59	4 (6.8)	21 (35.6)	23 (39.0)	11 (18.6)	0.061†
Lymphovascular invasion						
Positive	7	1 (14.3)	3 (42.9)	2 (28.5)	1 (14.3)	
Negative	72	3 (4.2)	20 (27.8)	34 (47.2)	15 (20.8)	0.337*
Tumor stage						
Ta	8	0 (0.0)	1 (12.5)	4 (50.0)	3 (37.5)	
T 1	54	1 (1.9)	17 (31.5)	24 (44.4)	12 (22.2)	
T 2	15	2 (13.3)	4 (26.7)	8 (53.3)	1 (6.7)	
T 3	2	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0.107*
Total	79	4 (5.1)	23 (29.1)	36 (45.6)	16 (20.2)	

*By Fisher's exact test. †By Chi square test.

https://doi.org/10.15218/zjms.2024.036

Discussion

GATA3, a member of GATA family transcription factors, is expressed in normal urothelial epithelium and urothelial carcinoma,[16, 19] and it has been recognized to have diagnostic and prognostic implications in bladder cancer patients. Along years, the value of GATA3 immunohistochemical expression in UC has been investigated by researchers, and has been concluded that it is a useful marker for urothelial carcinoma, as it has been valuable in confirming the urothelial origin of metastatic UC, as being a significant marker for primary UC.[11,14,21,25,26] In various studies , variable expressions of GATA3 for UC were reported, ranged from 77% to up to 99%.[18-21, 25-27] In the present study, GATA3 was expressed in 94.9% of cases, Comparable results were obtained by other studies, as Abdullah et al. from Iraq[20] recorded GATA3 expression in 96% of their studied cases, Leivo et al. and Clark et al.[26, 27] in 99% and 95%, respectively. While GATA3 expressed in 77% of cases in a study was done by Agrawal et al,[18] 80% by Chang et al,[21] 80.15% by Naik et al,[19] and 83.5% by Hoang et al.[25] This discrepancy in results can be explained by the differences in sample size, variable antibody sources, and different properties of antibodies.

This study showed reduction in GATA3 expression in UC in comparison to normal urothelium, as in the cases in which normal urothelium was presented in the sample, GATA3 expressed in all (100%) those normal urothelium, this result was in alignment with that observed by Naik et al.[19] and Miyamoto et al,[16] who revealed GATA3 positivity in 100% and 98% of normal urothelium respectively. Whereas, in the studied UC cases, GATA3 showed positivity in 94.9% of cases, this down-expression of GATA3 in UC in comparison to normal urothelial tissue was also recorded by other studies.[12, 16, 17, 19]

The study revealed that the mean age of the patients (SD) was 68.1 (10.9) years, majority (77.2%) were aged more than 60 years, similar to what has been reported by Abdullah et al.[20] There was no significant association between GATA3 expression and patients' age, this result was in alignment to that observed by Wang et al.[12] Sixty-one males and eighteen females were included in this study, majority (77.2%) were males, comparable to what was recorded by Abdullah et al.[20] and others,[26, 28] this male predominance may be attributed to the more prevalence of tobacco smoking and occupational exposure to chemical carcinogens among males, which are major risk factors for UC. No significant association was detected between GATA3 expression and gender of the patients; this coincides with a study was done by Wang et al.[12]

This study showed higher expression of GATA3 in papillary UC than in non-papillary UC cases, as GATA3 positivity was recorded in 97.1% of papillary UC cases, whereas 80% of non-papillary UC cases expressed GATA3, this result was in harmony with what was obtained by Naik et al,[19] who recorded GATA3 positivity in 97.5% and 76.27% of papillary UC and non-papillary UC cases respectively. Additionally, in this study, the majority (71%) of papillary UC cases were moderate to strongly immunoreactive for GATA3, while half of non-papillary UC cases showed weak immunoreactivity for GATA3, and 20% did not show any reactivity for the antibody. Results showed that there was a statistically significant association between GATA3 expression and the tumor pattern, comparable to that observed by other studies.[12,17, 19]

In the present study, all low-grade UC cases expressed GATA3, while high-grade UC cases showed a decrease in expression, the down-expression of GATA3 in high-grade cases were also recorded by other studies.[16, 18, 19] Moreover, among the studied cases, 90% of low-grade UC cases showed moderate to strong immunoreactivity for GATA3, whereas, more than one third of high-grade UC cases were weakly immunoreactive

for GATA3. There was no significant association between GATA3 expression and tumor grade, similar to what was obtained by other studies.[12,20]

This study revealed reduction in GATA3 immunoreactivity in those cases which have lympho-vascular invasion (LVI), as more than half of the cases which have LVI, were weakly immunoreactive for GATA3 or did not show any reactivity. This result was not found to be statistically significant, similar to what was obtained by Agrawal et al.[18]

Furthermore, when GATA3 positivity compared in non-invasive UC to invasive UC cases (LP invasive UC and muscle invasive UC), the results of this study showed that GATA3 expressed in all (100%) cases of non-invasive UC, whereas its expression reduced in invasive UC cases, as 94.36% of cases were positive for GATA3, this reduction in GATA3 expression in invasive UC in comparison to non-invasive UC cases was also recorded by other studies.[18-20] As well, in comparing GATA3 expression in non-invasive UC to LP invasive UC to muscle invasive UC individually, results of this study showed higher GATA3 expression in non-invasive UC than in LP invasive UC, and higher expression in LP invasive UC than muscle invasive UC, as GATA3 expressed in 100%, 98.1% and 82.35% of non-invasive UC, LP invasive UC and muscle invasive UC cases respectively, similar results were obtained by other studies.[18, 19]

Additionally, this study showed decrease GATA3 immunoreactivity in muscle invasive UC in comparison tonon-muscle invasive UC (non-invasive UC, LP invasive UC), as two third of non-muscle invasive UC cases showed moderate to strong immunoreactivity for GATA3, while nearly half of the muscle invasive UC cases showed only weak positivity for GATA3, or did not show any reactivity, these findings were in concordance with those obtained by others.[18] No significant association was found between GATA3 expression and tumor stage, which was similar to what was observed by Abdullah et al.[20]

Conclusion

This study concluded that GATA3 is a useful diagnostic immunohistochemical marker for urothelial carcinoma, as this marker was expressed in 94.9% of UC cases with a significant association with tumor pattern. Further studies are required to evaluate GATA3 expression in association with urothelial cancer progression and metastasis.

Funding

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin 2018; 68(6):394–424. https://doi.org/10.3322/caac.21492
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin 2021; 71(3):209–49. https://doi.org/10.3322/caac.21660
3. Hussain AM, Lafta RK. Cancer Trends in Iraq 2000–2016. Oman Med J 2021; 36(1):e219. https://doi.org/10.5001%2Fomj.2021.18
4. Khoshnaw N, Mohammed HA, Abdullah DA. Patterns of cancer in Kurdistan-results of eight years cancer registration in Sulaymaniyah Province-Kurdistan-Iraq. Asian Pac J Cancer Prev 2016; 16(18):8525–31. https://doi.org/10.7314/APJCP.2015.16.18.8525
5. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of bladder cancer. Med Sci 2020; 8(1):15. https://doi.org/10.3390/medsci8010015
6. McConkey DJ, Lee S, Choi W, Tran M, Majewski T, Lee S, et al. Molecular genetics of bladder cancer: Emerging mechanisms of tumor initiation and progression. Urol Oncol 2010; 28(4):429–40. https://pubmed.ncbi.nlm.nih.gov/20610280/
7. Wu G, Wang F, Li K, Li S, Zhao C, Fan C, et al. Significance of TP53 mutation in bladder cancer disease progression and drug selection. Peer J 2019; 7:e8261. https://doi.org/10.7717/peerj.8261

8. Roperch J-P, Grandchamp B, Desgrandchamps F, Mongiat-Artus P, Ravery V, Ouzaid I, et al. Promoter hypermethylation of HS3ST2, SEPTIN9 and SLIT2 combined with FGFR3 mutations as a sensitive/specific urinary assay for diagnosis and surveillance in patients with low or high-risk non-muscle-invasive bladder cancer. BMC Cancer 2016; 16(1):1–9. https://doi.org/10.1186/s12885-016-2748-5
9. Miettinen M, Cue PAM, Sarlomo-Rikala M, Rys J, Czapiewski P, Wazny K, et al. GATA 3–a multispecific but potentially useful marker in surgical pathology–a systematic analysis of 2500 epithelial and non-epithelial tumors. Am J Surg Pathol 2014; 38(1):13. https://doi.org/10.1097%2FPAS.0b013e3182a0218f
10. Asch-Kendrick R, Cimino-Mathews A. The role of GATA3 in breast carcinomas: a review. Hum Pathol 2016; 48:37–47. https://doi.org/10.1016/j.humpath.2015.09.035
11. Liu H, Shi J, Wilkerson ML, Lin F. Immunohistochemical Evaluation of GATA3 Expression in Tumors and Normal Tissues A Useful Immunomarker for Breast and Urothelial Carcinomas. Am J Clin Pathol 2012; 138(1):57–64. https://doi.org/10.1309/AJCP5UAFMSA9ZQBZ
12. Wang C, Yang S, Jin L, Dai G, Yao Q, Xiang H, et al. Biological and clinical significance of GATA3 detected from TCGA database and FFPE sample in bladder cancer patients. Onco Targets Ther 2020; 13:945. https://doi.org/10.2147/OTT.S237099
13. Hosoya T, Maillard I, Engel JD. From the cradle to the grave: activities of GATA-3 throughout T-cell development and differentiation. Immunol Rev 2010; 238(1):110–25. https://doi.org/10.1111/j.1600-065X.2010.00954.x
14. Higgins JP, Kaygusuz G, Wang L, Montgomery K, Mason V, Zhu SX, et al. Placental S100 (S100P) and GATA3: markers for transitional epithelium and urothelial carcinoma discovered by complementary DNA microarray. Am J Surg Pathol 2007; 31(5):673–80. https://doi.org/10.1097/01.pas.0000213438.01278.5f
15. Li Y, Ishiguro H, Kawahara T, Miyamoto Y, Izumi K, Miyamoto H. GATA3 in the urinary bladder: suppression of neoplastic transformation and down-regulation by androgens. Am J Cancer Res 2014; 4(5):461. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4163611/?report=reader#
16. Miyamoto H, Izumi K, Yao JL, Li Y, Yang Q, McMahon LA, et al. GATA binding protein 3 is down-regulated in bladder cancer yet strong expression is an independent predictor of poor prognosis in invasive tumor. Hum Pathol 2012; 43(11):2033–40. https://doi.org/10.1016/j.humpath.2012.02.011
17. Kamel NA, Abdelzaher E, Elgebaly O, Ibrahim SA. Reduced expression of GATA3 predicts progression in non–muscle invasive urothelial carcinoma of the urinary bladder. J Histotechnol 2020; 43(1):21–8. https://doi.org/10.1080/01478885.2019.1667126
18. Agarwal H, Babu S, Rana C, Kumar M, Singhai A, Shankhwar SN, et al. Diagnostic utility of GATA3 immunohistochemical expression in urothelial carcinoma. Indian J Pathol Microbiol 2019; 62(2):244. https://doi.org/10.4103/ijpm.ijpm_228_18
19. Naik M, Rao BV, Fonseca D, Murthy SS, Giridhar A, Sharma R, et al. GATA-3 expression in all grades and different variants of primary and metastatic urothelial carcinoma. Indian J Surg Oncol 2021; 12(1):72–8. https://doi.org/10.1007/s13193-019-01026-0.
20. Abdullah W, Kerbel H, Husseini R. Applying gata3 in differentiating urothelial carcinoma from prostatic adenocarcinoma: An immunohistochemical study. Asian J Pharm Clin Res 2018; 11(12):292–5. https://doi.org/10.22159/ajpcr.2018.v11i12.28232.
21. Chang A, Amin A, Gabrielson E, Illei P, Roden RB, Sharma R, et al. Utility of GATA3 immunohistochemistry in differentiating urothelial carcinoma from prostate adenocarcinoma and squamous cell carcinomas of the uterine cervix, anus, and lung. Am J Surg Pathol 2012; 36(10):1472. https://doi.org/10.1097%2FPAS.0b013e318260cde7
22. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs—part B: prostate and bladder tumours. Eur Urol 2016; 70(1):106–19. https://doi.org/10.1016/j.eururo.2016.02.028.
23. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017; 67(2):93–9. https://doi.org/10.3322/caac.21388
24. Liang Y, Heitzman J, Kamat AM, Dinney CP, Czerniak B, Guo CC. Differential expression of GATA-3 in urothelial carcinoma variants. Hum Pathol 2014; 45(7):1466–72. https://doi.org/10.1016/j.humpath.2014.02.023
25. Hoang LL, Tacha D, Bremer RE, Haas TS, Cheng L. Uroplakin II (UPII), GATA3, and p40 are highly sensitive markers for the differential diagnosis of invasive urothelial carcinoma. Appl Immunohistochem Mol Morphol 2015; 23(10):711–6. https://doi.org/10.1097/PAI.0000000000000143.
26. Leivo MZ, Elson PJ, Tacha DE, Delahunt B, Hansel DE. A combination of p40, GATA-3 and uroplakin II shows utility in the diagnosis and prognosis of muscle-invasive urothelial carcinoma. Pathology 2016; 48(6):543–9. https://doi.org/10.1016/j.pathol.2016.05.008

https://doi.org/10.15218/zjms.2024.036

27. Clark BZ, Beriwal S, Dabbs DJ, Bhargava R. Semiquantitative GATA-3 immunoreactivity in breast, bladder, gynecologic tract, and other cytokeratin 7–positive carcinomas. Am J Clin Pathol 2014; 142(1):64–71. https://doi.org/10.1309/AJCP8H2VBDSCIOBF.
28. Bahria-Sediki IB, Yousfi N, Paul C, Chebil M, Cherif M, Zermani R, et al. Clinical significance of T-bet, GATA-3, and Bcl-6 transcription factor expression in bladder carcinoma. J Trans Med 2016; 14(1):1–11. https://doi.org/10.1186/s12967-016-0891-z