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Short Communication

Galectin-3 marker expression in renal cell carcinoma and correlation with patient's clinicopathologic factors: A cross-sectional study

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Abstract

Background: Renal Cell Carcinoma is one of the most common malignancies worldwide. To date, multiple attempts had been made to accurately diagnose it and predict its behavior. One of the most intriguing biomarkers that have been assessed since 90s, is galectin-3. This study aimed to increase the prior knowledge of galectin-3 expression association with patient's clinicopathologic factors.

Methods: In this single-center cross-sectional study, 71 patient samples from hospital archive were assessed for galectin-3 expression by immunohistochemistry assay. Pathologic slides were evaluated for histologic subtype, grade, stage, tumor size, presence of necrosis, and invasion of the renal vein. By adding cytoplasmic staining score to the color intensity score, a final score was recorded as galectin-3 positivity score.

Results: 88 pathological slides of patients with confirmed RCC were screened and 71 were finally assessed. The mean age of the patients was 58.52 years (lowest 30 and highest 87). 67.6% were males and 32.4% were females. 68% of tumors were clear cell carcinoma, and only one oncocytoma was present. All 9 chromophobe cases showed a strong galectin-3 expression. Except for female gender (47.8% vs 18.8% in men; P=0.01), no statistically significant association was found between patient age, tumor grade, tumor size, tumor stage, and renal vein invasion with the level of galectin-3 expression.

Conclusion: Considering the contradictory findings between this study and other similar studies, it can be concluded that the physiological role of galectins is very complex and the need for larger and more comprehensive evaluations is felt.

Keywords: Galectin-3, Kidney neoplasms, Galectins.

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Renal cell carcinoma (RCC) is the seventh most common malignancy worldwide. In 2018, nearly 65,340 new cases with 14,970 associated deaths were reported in the United States (1). Galectin-3 expression has recently emerged as a potential diagnostic and/or prognostic marker for some cancers of which the results are especially encouraging in thyroid cancers (2, 3).

Previous studies about galectin-3 expression and renal cell carcinoma have led to conflicting results; most proposed an increased expression and worse prognosis in RCC, while some proposed the opposite (4-6). In this study, we tried to investigate the amount of galectin-3 expression in renal cell carcinoma and its relationship with the clinical and pathological factors of patients (i.e., age, sex, pathologic subtype, grade, stage, tumor size, presence of necrosis, and invasion of the renal vein).

Methods

This was a cross-sectional study of patients with renal cell carcinoma who underwent either a total or partial nephrectomy between 2016 and 2021 in Shahid Beheshti Hospital, Babol, Iran. Samples of patients were collected from hospital archive and were excluded if a neoadjuvant treatment was recorded, did not include normal renal cells, or was not enough for immunohistochemistry (IHC) analysis. The main outcome variable was galectin-3 expression based on IHC. Other variables collected were age, sex, pathologic subtype, grade, stage, tumor size, presence of necrosis, and invasion of the renal vein all of which were assessed in pathologic slides by using direct light microscopy. Formalin-fixed, paraffin-embedded (FFPE) blocks were stained for galectin-3 using immunoperoxidase staining and Labeled Streptavidin–Biotin (LSAB) staining methods, after 5µ thickness tissue cutting by microtme on charged slides. The kits were manufactured by the American MEDAYSIS company and were diluted in 1:100 ratio using papillary thyroid cancer tissues as control. The slides were assessed by an optical microscope (Olympus BX-41, at X100 and X400 magnification) by two independent pathologists unaware of patients' history and the estimated percentage of stained tumor cells it was taken and expressed. Slides were investigated in three staining "hotspots" and were rated to be strongly positive, moderately positive, weakly positive, and negative if cytoplasmic staining was over 75 % (score=4+), 51%-75 % (score=3+), 11-50 % (score=2+), and below 10 % (score=1+) respectively.

Also the strength of staining was rated separately as +3 score for brown, +2 for pale brown, +1 for light brown, and zero for no stain. By adding these two scores, a final score was calculated and slides were categorized as "strongly positive" with score 6-7, "fairly positive" with score 4-5, weakly positive with score 2-3, and negative with score 0-1 (figure 1). Assuming a positive galectin-3 staining of 90%, the sample size was estimated to be at least 71 patient using below formula (with a d=0.07 and type 1 error of 0.05). Available sampling was used. Quantitative variables were not categorized. Sample size equation:

$$\frac{Z^2_{1-\frac{\alpha}{2}} P(1-P)}{d^2}$$

Data were analyzed using IBM SPSS Statistics software (Version 27). To assess relation between outcome and continuous variable, t-test and ANOVA was utilized. Relationship of dichotomous variables and outcome was assessed by Pearson's chi-square test. A p-value of less than 0.05 was considered significant.

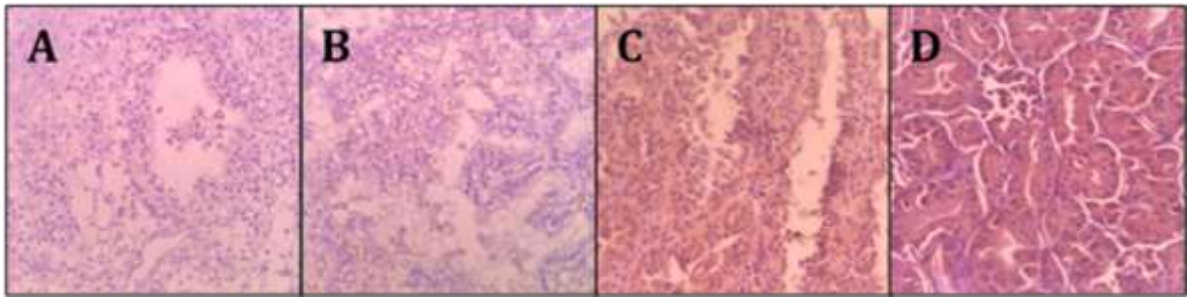

Figure 1. Galectin-3 Immunohistochemistry cytoplasmic staining scores. A, negative staining; B, weakly positive; C, moderately positive; D, Strong positive

Results

In this study, 88 pathological slides of patients with confirmed RCC were screened and 71 were examined for the analysis. Galectin-3 expression was significantly different between tumor types (strong expression being 20.8% in clear cell carcinoma, 0% in papillary cell carcinoma, and 100% in chromophobe carcinoma and oncocytoma; P=0.02). All 9 cases of chromophobe RCC showed strong positive staining. In contrast, only 7.7% of papillary cancers showed a strong or fairly positive staining (score 4-7) for galectin-3. 54% of clear cell tumors had a strong or fairly positive staining and the oncocytoma was also strongly positive. Sex was associated with galectin-3 expression, as 47.8% of female patients were strongly positive compared to 18.8% for men (P=0.01). Strong positive score was seen in 21%, 60%, and 15% of patients with G1, G2, and G3 cancers respectively (P=0.29). No significant association was found between tumor grade and galectin-3 expression. Tumor stage was also not associated with galectin-3 expression, as T1a, T1b, T2a, T2b, and T3 tumor were strongly positive in 20%, 23%, 67%, 20%, and 18% of cases respectively (P= 0.24). Renal vein invasion (RVI) and necrosis also were not associated with galectin-3 expression. Strong positive score was seen in 21% of those with RVI and 30% of those without RVI (P=0.35) and 36% of those with necrosis and 21% of those without necrosis

(P=0.36). There were no associations between tumor size and galectin-3 expression (p=0.62).

Discussion

Our results showed that women express galectin-3 more likely than men (48% vs 19%). Similarly, Aboulhagag et al.'s proposed that the expression of galectin-3 might be higher among women, although not statistically significant (P=0.145) (7). In contrast, von Klot et al. reported higher expression of galectin-3 in males (8). Keeping in mind that galectin-3 coding region is not located on sex chromosomes, it seems that this inconsistency is likely attributed to chance and would only resolve if a large sample size from different races is achieved. Tumor grade and stage were not associated with galectin-3 expression in our study. This is in contrast to a previous study showing a higher grade in those with higher expression (9). Robust data on stage and grade association with galectin-3 expression is scarce and conflicting, as some articles have claimed a higher stage (10) and some lower stage and metastases (11) in lower expressers. The lack of galectin-3 expression was seen more among samples with RVI, but this difference was not statistically significant (P=0.346). In similar studies, similar results were obtained and no positive or negative correlation was reported (12, 13). We found no significant difference between the expression level of galectin-3 among samples with and without necrosis while other studies such as that conducted by Aboulhagag et al., found an inverse relationship between galectin-3 expression and the presence of tumor necrosis and bleeding. According to their results, the high expression of galectin-3 in normal kidney tissue and its low expression in tumors with hemorrhage and necrosis indicate the tumor suppressive role of galectin-3 in RCC (7). In the present study, no statistical significant association was found between patient age, tumor grade, tumor size, tumor stage, and renal vein invasion with the level of galectin-3 expression. The only statistically significant relationship found was between gender and galectin-3 expression level (P=0.01); Galectin-3 expression was higher among women. Based on this and similar studies, it can be concluded that the physiological role of galectins is very complex and the need for larger and more comprehensive evaluations is felt.

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Authors' contribution: Dr Ghodsieh Kamrani, Dr Mohammad Ranaee, Dr Reza Havaspoor, and Dr Hamid Shafi have contributed in study design, sample collection, data collection and writing the manuscript. Dr Davoud Jahansouz and Mr Mohammad Ebrahim Sohrabi contributed to study design, data collection and writing the manuscript. Dr Hoda Shirafkan contributed in study design, methodology, data collection and analysis, and writing the manuscript.

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