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Research Article

Monoclonal Gammopathy of Undetermined Significance is Not Associated with Renal Cell Carcinoma

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Abstract

Objectives: The aim of this study was to investigate monoclonal gammopathy of undetermined significance (MGUS) in patients with renal cell carcinoma (RCC) and compare to healthy individuals.

Methods: This was a case-control study conducted between July 2022 and December 2022 including 68 patients with RCC and 47 healthy controls.

Results: The median age of control group was 67 (51-75) years and that of the RCC group was 59 (51-69.5) (p=0.039). Sex distributions were similar in the two groups. RCC disease duration was 24 (12-60) months. The albumin, calcium, hemoglobin, hematocrit levels, and lymphocyte (p<0.001 for all) and platelet counts (p=0.017) were significantly higher in the RCC group compared to controls. There was no significant difference between the groups in terms of the number of the patients with MGUS (p=0.512), monoclonal band positivity (p=0.512), abnormal bands positivity (p=0.080) and median gammaglobulin level (p=0.774).

Conclusion: The present study shows no evidence for increased MGUS incidence in patients with RCC; however, more comprehensive studies are required to clarify these findings in different populations and determine the potential roles of other factors in the relationship between RCC and MGUS.

Keywords: Renal cell carcinoma, monoclonal gammopathy of undetermined significance, immunofixation, protein, electrophoresis

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Renal cell carcinoma (RCC) is the most common solid lesion of the kidney and accounts for approximately 90% of all kidney cancers and 3% of all cancers,[1,2] with a 2% annual increase in incidence.[1,2] Many patients with RCC present with symptomatic disease in advanced stages, but a considerable proportion are diagnosed incidentally via imaging performed for other reasons.[3]

Monoclonal gammopathy occurs due to the production of monoclonal immunoglobulin as a result of clonal proliferation of the B lineage of lymphocytes.[4] Hematological disorders presenting with monoclonal gammopathy are many, including monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, lymphomas, and Waldenström macroglobulinemia.[4,5] MGUS is the most common and demonstrates a higher frequency after 50 years of age, and it has been reported to lead to lymphoid malignancies, non-Hodgkin lymphomas, and multiple myeloma.[6] However, since the risk excessively low (around 1%), MGUS is considered to be benign.[4,7] However, MGUS has been associated with shorter life expectancy, increased

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risk of fractures, kidney failure, peripheral neuropathy, secondary immunodeficiency, and a number of comorbid conditions, including cardiovascular diseases.[6] Also, concomitant renal mucosa associated lymphoid tissue (MALT) lymphoma[8] and RCC[9] cases seen in patients with MGUS have been published and an increased risk of coexistence of prostate cancer and MGUS has been reported previously.[10-12] However, evidence pertaining to the associations between MGUS and RCC have remained at the case report level,[9] and the associations have not yet been directly investigated.

Patients with RCC should be followed carefully for secondary malignancies. Considering the aforementioned association of RCC and hematological malignancies, especially multiple myeloma and non-Hodgkin lymphoma, it is highly likely that the coexistence of these cancers could adversely affect prognosis. However, there is no definitive data on whether there is a causal relationship between them.[6] We postulated that there may be a causal relationship between MGUS, which is a precursor for some RCC-associated malignancies, and RCC. Therefore, in this study, we aimed to investigate whether the frequency of MGUS in patients with RCC is different from healthy individuals and whether there is a significant relationship between RCC and MGUS.

Methods

Study Design, Setting and Ethical Considerations

This was a case-control study conducted as joint research by the Departments of Urooncology outpatient clinic between July 2022 and December 2022. The study was designed with respect to all relevant ethical considerations and was carried out according to the Declaration of Helsinki and its later amendments. The local ethics committee approved the research plan (Decision date: 04.07.2022, decision no: 2022-13-03). All participants signed written informed consent forms after receiving detailed explanation about the study and accepting to participate.

Participants

The study included 68 patients with a diagnosis of RCC followed in the Urooncology departments on the relevant dates and 47 healthy volunteers randomly selected from the patients who applied to the urology outpatient clinic for any reason. Patients who were diagnosed with any monoclonal gammopathy other than MGUS, subjects with symptoms associated with multiple myeloma or Waldenström macroglobulinemia, those with other known malignancy, and individuals unwilling to participate in the study were excluded. For the control group, those with any current or prior comorbidities or malignancies were excluded.

The diagnosis and treatment of RCC was performed in accordance with The European Association of Urology guidelines on RCC recommendations.[1,13]

Data Collection and Measurements

Laboratory Analysis

Blood biochemistry and complete blood count results, including hemoglobin, hematocrit, mean corpuscular volume levels, white blood cell, lymphocyte, neutrophil, platelet counts, and creatinine, albumin and calcium levels, were measured from blood samples drawn routinely after subjects volunteered to participate in the study. All analyses were performed in the certified local biochemistry laboratory with calibrated devices (Roche COBAS Integra 800, Roche Diagnostics, USA; and CAL-8000, Mindray, China) and commercial test kits, according to manufacturer recommendations.

Gammopathy Related Measurements and Tools

MGUS was defined by the presence of monoclonal proteins (M-protein) produced by a small B-cell/plasma cell clone.[14] Evidence of a monoclonal band in the gamma region was investigated by protein electrophoresis (Capillarys 2, Sebia, UK). Subsequently, abnormal band positivity and immunoglobulin isotype was determined by immunofixation electrophoresis (Capillarys 2, Sebia, UK). Bone marrow biopsy was performed in participants who had abnormal bands in immunofixation electrophoresis. MGUS was diagnosed by an M-protein lower than 30 g/L in serum and less than 10% of plasma cells in bone marrow (if bone marrow biopsy is performed) in the absence of myeloma-related symptoms (for non-IgM MGUS diagnosis) or less than 10% of lymphoplasmacytic cells in the bone marrow (if bone marrow biopsy is performed) in the absence of Waldenström macroglobulinemia related symptoms (for IgM MGUS diagnosis).[14]

Furthermore, quantitative gammaglobulin levels were determined by protein electrophoresis. According to the manufacturer's manual, the reference range for gammaglobulin was 8-13 g/dL. Participants were classified according to gamma globulin level as subjects with hypogammaglobulinemia (gammaglobulin level <8 g/dL), normal (gammaglobulin between ≥8 g/dL and ≤13 g/dL) and hypergammaglobulinemia (gammaglobulin level >13 g/dL).

Statistical Analysis

The classical $p<0.05$ significance threshold was used for all analyses. Data were collected into an SPSS database and all analyses were performed on the IBM SPSS software (version 25.0, IBM, NY, USA). For the normality check, the Kolmogorov-Smirnov test was used. Continuous data conforming to parametric assumptions and meeting normal distribution characteristics were described with mean±standard deviation; otherwise, median (1^{st} quartile - 3^{rd} quartile) were used. Discrete variables were summarized with frequency (percentage). Normally distributed variables were analyzed with the Student's t-test. Non-normally distributed variables

were analyzed with the Mann-Whitney U test. Categorical variables were analyzed with appropriate chi-square tests or the Fisher's exact test. Multivariable logistic regression was performed to evaluate independent relationships between MGUS, protein electrophoresis results, immunofixation electrophoresis results, gamma globulin level and RCC, after adjusting for age and sex.

Results

The median age of control group was 67 (51 - 75) years and that of the RCC group was 59 (51 - 69.5) (p=0.039). Males represented 57.45% (n=27) of the control group and 45.59% (n=31) of the RCC group (p=0.289). The median duration with RCC was 24 (12 - 60) months ın the patient group. Albumin, calcium, hemoglobin, hematocrit levels and lymphocyte counts (p<0.001 for all) and mean platelet counts (p=0.017) were significantly higher in the RCC group than in controls. Two participants met the MGUS diagnostic criteria and both were in the RCC group. However, there was no significant difference between the groups in terms of the number of the patients with MGUS (p=0.512).

According to the protein electrophoresis results, monoclonal band positivity was detected in 2 (2.94%) patients in the RCC group, while monoclonal band positivity was not detected in any of the subjects in the control group (p=0.512). According to immunofixation electrophoresis results, abnormal bands were detected in 8 (11.76%) subjects in the RCC group and in 1 (2.13%) subject in the control group (p=0.080). All patients with abnormal bands in the RCC group had monoclonal IgG Kappa, while the subject in the control group had monoclonal IgG Lambda. Bone marrow results showed hypercellular patterns and revealed 5% atypical plasma cells. The bone marrow of the participant in the control group showed normocellular pattern and 2% atypical plasma cells. There was no significant difference between the groups in terms of median gamma globulin level (p=0.774) and gammaglobulin class distribution (p=0.786) (Table 1).

Table 1. Summary of demographics and measurements with regard to groups

	Groups		
	Control (n=47)	**RCC (n=68)**	**p**
Age (years)	67 (51 - 75)	59 (51 - 69.5)	0.039
Sex			
Male	20 (42.55%)	37 (54.41%)	0.289
Female	27 (57.45%)	31 (45.59%)	
Duration of RCC (months)	-	24 (12 - 60)	-
Creatinine (mg/dL)	0.99 (0.73 - 1.17)	1.00 (0.78 - 1.17)	0.495
Albumin (g/dL)	3.40 (3.00 - 4.00)	4.71 (4.50 - 4.91)	<0.001
Calcium (mg/dL	8.8 (8.2 - 9.32)	9.5 (9.2 - 9.8)	<0.001
Hemoglobin (g/dL)	10.0 (8.5 - 12.1)	13.9 (12.45 - 14.75)	<0.001
Hematocrit (%)	30.8 (27.0 - 36.3)	41.6 (38.3 - 44.55)	<0.001
MCV (fl)	87.9 (82.3 - 92.1)	90.0 (85.45 - 92.8)	0.171
WBC ($x10^3$)	7.95 ± 3.56	7.91 ± 2.17	0.944
Lymphocyte ($x10^3$)	1.58 (1.19 - 2.00)	2.14 (1.64 - 2.68)	<0.001
Neutrophil ($x10^3$)	4.71 (3.21 - 6.50)	4.79 (3.52 - 5.62)	0.716
Platelet ($x10^3$)	220.37 ± 109.34	264.56 ± 69.38	0.017
MGUS	0 (0.00%)	2 (2.94%)	0.512
Monoclonal band positivity in the protein electrophoresis	0 (0.00%)	2 (2.94%)	0.512
Abnormal band positivity in the immunofixation electrophoresis	1 (2.13%)	8 (11.76%)	0.080
IgG Lambda	1 (2.13%)	0 (0.00%)	
IgG Kappa	0 (0.00%)	8 (11.76%)	
Gamma globulin level (g/dL)	10.2 (8.6 - 14.5)	10.9 (8.4 - 12.8)	0.774
Hypogammaglobulinemia	8 (17.02%)	12 (17.65%)	0.786
Normal	26 (55.32%)	41 (60.29%)	
Hypergammaglobulinemia	13 (27.66%)	15 (22.06%)	

Data are given as mean±standard deviation or median (1^{st} quartile - 3^{rd} quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. IgG: Immunoglobulin; MCV: Mean corpuscular volume; MGUS: Monoclonal gammopathy of undetermined significance; RCC: Renal cell carcinoma; WBC: White blood cell.

According to the results of the logistic regression analysis, no significant relationship was found between RCC and the presence of MGUS, monoclonal band positivity, abnormal bands, gamma globulin level and class, neither in unadjusted nor adjusted (age and sex) analyses (Table 2).

Discussion

Causal relationships between monoclonal gammopathy and a wide variety of pathological conditions in different organ systems have been reported.[4] Adequate investigation of these and other relationships could lead to new pathophysiological links that may allow the development of new treatment strategies.[4] The relationship between RCC and some monoclonal gammopathies, including multiple myeloma and some lymphoma subtypes, has been investigated previously. However, the association of MGUS with RCC has not been investigated. Our results showed that there were no significant relationships between RCC and the presence of MGUS, M-protein, abnormal bands and gammaglobulin levels.

Monoclonal gammopathy is usually detected incidentally in routine biochemical analyses. As a result of the acceleration of screening for diseases such as anemia and renal failure, gammaglobulin levels are being ordered at a higher frequency, which has led to an increase in the incidence of monoclonal gammopathy in recent years. This situation has enabled the investigation of the possible or definite relationships of monoclonal gammopathy with many diseases and cancers.[4,15] Although we found significant differences between RCC and control groups in terms of albumin, calcium, hemoglobin and hematocrit levels, and lymphocyte and platelet counts, both univariate and multivariate analyses showed that the RCC and control groups were similar in terms of MGUS presence, M-protein and abnormal bands and gammaglobulin levels. Although it could be suggested that this was a result of limited patient counts in the study, the incidence of MGUS in RCC patients was found to be 2.94%, which is very close to the MGUS frequencies reported for healthy populations.[6]

The relationship between monoclonal gammopathy and various malignancies has been investigated in various studies.[8,10-12] Peces et al. presented a case of MALT B cell lymphoma with kidney damage in a patient with monoclonal gammopathy. In this case, it was emphasized that monoclonal gammopathy IgM kappa persisted despite chemotherapy and rituximab treatment, and monoclonal gammopathy might be one of the advanced prognostic factors.[8] Some studies have shown an association between MGUS and the risk of different types of solid cancer, such as prostate cancer.[10-12] In a population-based study, MGUS was associated with prostate cancer, presenting a hazard ratio of 2.00 and independent from common risk factors.[8] Bonilla et al. recently presented a case of crystalcryoglobulinemia presenting with skin purpura, peripheral neuropathy, and acute kidney injury in a patient with accompanying clear cell RCC and this was the first case of concomitant RCC and crystalcryoglobulinemia in the literature.[9] Cryoglobulinemia is characterized by the presence of abnormal immunoglobulins in the serum that precipitate at temperatures below 37°C and become insoluble at higher concentrations. The resulting crystals can accumulate in various organs and tissues, primarily the skin and kidneys.[16,17] In this case,[9] following RCC excision and monoclonal gammopathy treatment, cryoglobulinemia did not re-occur in the 32-week follow-up. The authors believed that cytokine production due to RCC could have stimulated plasma cell replication, leading to monoclonal immunoglobulin production.[9] Also, crystalcryoglobulinemia has been reported in association with multiple myeloma.[9] Of the 40 cases with multiple

Table 2. Odds ratios for RCC, logistic regression analysis results

	Unadjusted		Adjusted (1)	
	OR (95% CI)	p	OR (95% CI)	p
MGUS	1150413903.242 (0 - N/A)	0.999	1028555814.661 (0 - N/A)	0.999
Monoclonal band positivity in the protein electrophoresis	1150413903.242 (0 - N/A)	0.999	1028555814.661 (0 - N/A)	0.999
Abnormal band positivity in the immunofixation electrophoresis	6.133 (0.741 - 50.794)	0.093	7.524 (0.879 - 64.386)	0.065
Gamma globulin level (2)		0.786		0.715
Hypogammaglobulinemia	0.951 (0.343 - 2.640)	0.923	1.082 (0.378 - 3.101)	0.883
Hypergammaglobulinemia	0.732 (0.300 - 1.783)	0.492	0.707 (0.282 - 1.769)	0.459

OR: Odds ratio; CI: Confidence interval; IFE: Immunofixation electrophoresis; (1) Adjusted with age and sex; (2) Reference category: Normal. MGUS: Monoclonal gammopathy of undetermined significance; RCC: Renal cell carcinoma

myeloma and RCC that were examined in the study,[9] 16 (40%) had simultaneous presentation, 14 (35%) had RCC before diagnosis of multiple myeloma, and 10 (25%) developed RCC after diagnosis of multiple myeloma. Three of the cases with simultaneous presentation demonstrated the presence of monoclonal plasma cells infiltrating the RCC or surrounding tissue.[18-20]

In a population-based study conducted by Ojha et al., the relationship between multiple myeloma and RCC was investigated. The results of this large epidemiological study showed that multiple myeloma occurred in 88 of 57,190 patients with RCC. Patients with RCC had higher overall relative risk of multiple myeloma compared to the general population, and this risk was highest among patients aged 50-59 years and within the first year after RCC diagnosis. From the other end of the relationship, RCC was found to have occurred in 69 of 34,156 patients with multiple myeloma. Patients with multiple myeloma had higher overall relative risk of RCC than the general population and this risk was highest among patients aged <50 years and within the first year after multiple myeloma diagnosis. It has been argued that the bidirectional relationship between these malignancies may be related to the common risk factors of RCC and multiple myeloma.[21] Apart from this comprehensive study, many other small-scale studies have also claimed a relationship between RCC and multiple myeloma.[22-24] The association of RCC and lymphoid malignancies, especially Non-Hodgkin Lymphoma, has also been reported frequently, but it has been argued that this association may be related to chemotherapy or radiotherapy.[25,26]

Synchronous or metachronous tumors are rare with RCC. An incidence of 3.7% of synchronous tumors with RCC has been demonstrated.[27] However, there are various confounding factors and conflicting explanations associated with this relationship.[21,22,28-30] However, the precise mechanism remains unclear. It is possible that immune function may be impaired in monoclonal gammopathies, even during the MGUS phase.[4] Studies have shown that patients with MGUS are at increased risk of infection due to immunodeficiency.[31,32] Considering the relationship between cancer and immunodeficiency,[33] it can be expected that there may be a cause-effect relationship between the immunodeficiency caused by MGUS and RCC. Plasma cell and RCC growth is dependent on cytokines, including Il-6.[4] Several studies have reported elevated serum IL-6 levels in patients with concomitant multiple myeloma and RCC.[30,34,35] In addition, IL-6 immunohistochemistry has been reported to be positive in patients with RCC.[36] On the other hand, RCCs have been shown to have mutations in c-Met. c-Met is a tyrosine kinase that binds hepatocyte growth factor, and hepatocyte growth factor has been claimed to potentiate IL-6-induced growth of myeloma cells.[37]

Renal impairment is associated with clonal plasma cell disorders, particularly multiple myeloma, and renal involvement has been associated with early death and shorter survival.[38,39] Recently, the term 'monoclonal gammopathy of renal significance' has been defined to distinguish nephrotoxic monoclonal gammopathies.[40] However, given the possibility of an alternative cause leading to renal dysfunction in patients with monoclonal gammopathy and the high prevalence of monoclonal gammopathy itself, there is also a perspective suggesting that the coexistence of renal dysfunction with monoclonal gammopathy of renal significance might be coincidental.[4] Current data is insufficient to establish a causal relationship between renal cancers and monoclonal gammopathies. In the present study, the frequency of MGUS in RCC patients was similar to literature-reported frequencies in healthy individuals. Nonetheless, it has been previously stated that monoclonal gammopathy can improve after RCC treatment.[9] That is, the participant features, design and results of this study make it difficult to make definitive conclusions about whether there is a relationship between RCC and MGUS. Therefore, in order to reach definite conclusions about the relationship between RCC and MGUS, there is a need for large population-based studies investigating the bidirectional relationship between RCC and MGUS.

To our knowledge, this is the first study to investigate the relationship between RCC and MGUS. However, the study has some limitations. The fact that it is a single-center study with relatively few participants limits the generalizability of its results, especially to other populations. Not all patients with RCC were included in the study due to various factors and the lack of non-routine investigations in some patients, and therefore, the number of participants was limited. The frequency of RCC was not investigated in patients with MGUS. Due to the limited number of patients with MGUS, the study was unable to investigate the prognostic impact of MGUS in association with RCC. This small sample size also posed challenges in exploring the relationship between different RCC subtypes and MGUS. The study included patients who were newly diagnosed with RCC, undergoing treatment, or in the follow-up phase after completing treatment. These factors collectively make it challenging to draw definitive conclusions regarding the relationship between RCC and MGUS based on the study's findings. Additionally, the lack of previously published similar studies hinders comprehensive discussion and comparison of the results.

Conclusion

In conclusion, the study found no significant difference in the occurrence of MGUS between the RCC and control groups examined in this study. Additionally, it must be noted that MGUS frequency was similar to the frequencies reported for the general population. However, it is important to note that this study did not demonstrate an increased incidence of MGUS in patients with RCC. Further comprehensive studies are necessary to investigate the potential relationships between MGUS and RCC, and the impact of other factors on this relationship.

Disclosures

Ethics Committee Approval: The study was designed with respect to all relevant ethical considerations and was carried out according to the Declaration of Helsinki and its later amendments. The Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approved the research plan (Decision date: 04.07.2022, decision no: 2022-13-03).

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