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## Our cases of monoclonal gammopathy renal significance (MGRS): Single center experience

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### Abstract

**Objective:** To analyze the clinical, pathological spectrum and prognosis of patients with Monoclonal Gammopathy of Renal Significance (MGRS).

**Methods:** Patients with kidney biopsy-proven MGRS at Dr Lütfi Kırdar City Hospital between 2015 and 2019 were included, clinical data, kidney pathology type, treatment and prognosis were collected.

**Results:** Thirteen patients, constituting 0.77% of kidney biopsies, were recorded. Eight MGRS patients had amyloidosis.

2 patients had monoclonal immunoglobulin deposition disease. 1 patient with proliferative glomerulonephritis with monoclonal immunoglobulin (G) deposits, 1 patient with cryoglobulinemic glomerulonephritis and one patient with C3 glomerulonephritis. All of our patients were treated with chemotherapy and/or stem cell transplantation. The mean follow-up period was  $26 \pm 34$  months. Multiple myeloma developed in one patient at 19 months during follow-up. At the end of the follow-up, 2 patients (%) died, 3 patients (%) developed End-Stage Renal Disease (ESRD).

**Conclusion:** MGRS is a rare form of hematological disorder that causes kidney damage presenting with a wide range of pathological lesions. Amyloidosis is the most common form. Early diagnosis and close follow-up are important because renal survival of MGRS patients can be improved with early treatment.

**Keywords:** monoclonal gamopathies; renal injury; proteinuria.

### Introduction

Monoclonal gammopathies are a group of diseases that are formed by the activation of plasma cells, in which plasma cells secrete a certain type of immunoglobulin called M protein. This accumulation may progress over time and cause organ damage. The most common form of monoclonal gammopathies, Monoclonal Gammopathy of Unknown Importance (MGUS), may be associated with premalignant and nonmalignant diseases. Its frequency increases with age. Its prevalence reaches 3% in the

population over the age of 50. Diagnosis is made by monitoring less than 10% plasma cells in the bone marrow [1].

Renal damage was observed in some of the patients with a diagnosis of MGUS followed, and it was observed that these patients did not meet the criteria for myeloma in the bone marrow evaluation [2,3]. Therefore, International Kidney and Monoclonal Gammopathy Research Group proposed to use the term Monoclonal Gammopathy (MGRS) with Renal Significance in 2012 [7]. This definition was suggested in patients with

MGUS who did not meet the criteria for multiple myeloma, and in the group of patients with secondary renal damage due to M protein [4-9].

Classification in MGRS is based on the type and distribution of monoclonal deposits:

**Organized:** Fibrillary deposits (Ig-associated amyloidosis (AL,AH,AHL), fibrillary glomerulonephritis); microtubular deposits (monoclonal cryoglobulinemia, immunotactoid glomerulopathy); crystal inclusions (light chain proximal tubulopathy, crystal-deposit histiocytosis) [10-14].

**Non-organized:** Ig-related (monoclonal immunoglobulin storage disease and monoclonal gammopathy-associated proliferative glomerulonephritis), non-Ig (C3 glomerulopathy with monoclonal gammopathy).

Most of the patients with MGRS are at risk of progressive renal disease and end-stage renal disease develops in later periods. In addition, the risk of recurrence is high in renal transplant. Therefore, aggressive treatment is recommended for these patients, unlike patients with MGUS who are only followed up with periodic follow-ups. Renal biopsy is mandatory in patients with MGUS with renal findings. In patients with MGRS, treatment is based on the type of renal injury and the immunoglobulin-producing b-cell clone. Eradication of monoclonal proliferating plasma cells should be aimed in treatment [15,16]. In this article, we reviewed the literature in company with our four patients diagnosed with MGRS, whom we followed in our outpatient clinic.

## Methods

The cases who underwent kidney biopsy and followed up in our hospital's Nephrology Outpatient Clinic between 2015 and 2019 were retrospectively analyzed. Patients with malignancy and patients with multiple myeloma overt bone marrow biopsy were not included in the study. Demographic characteristics such as age, gender, basal creatinine and post-treatment creatinine, additional diseases and habits, treatments and renal biopsy results of cases with MGRS were recorded.

Our study is a retrospective study and descriptive statistics were performed using SPSS software (SPSS Inc, Chicago, IL) version 16.0. Variables were defined as the mean standard deviation. Variables that did not show normal distribution were defined as median (min-max). Bone marrow biopsy was performed in all patients to exclude multiple myeloma. Renal survival and overall survival of the patients were evaluated.

Renal biopsies were evaluated by experienced pathologists by light microscopy and immunofluorescence examination.

## Results

**Clinical and demographic pathological data:** Thirteen patients, constituting 0.77% of kidney biopsies, were recorded. 4 out of 13 patients were women. The mean age of the patients was  $48 \pm 12$  years. Eight MGRS patients had amyloidosis (62%). Two patients had monoclonal immunoglobulin deposition disease. 1 patient with proliferative glomerulonephritis (MPGNID) with monoclonal immunoglobulin (G) deposits, 1 patient with

cryoglobulinemic glomerulonephritis and 1 patient with C3 glomerulonephritis. The mean 24-hour proteinuria level was 6560 mg/day. His serum albumin level was 2.8 gr/dl. The mean creatinine level was 5.2 mg/dl. The mean e GFR level was 57 ml/min. Two patients were undergoing hemodialysis at the time of diagnosis. After treatment, one patient was weaned from hemodialysis. 5 patients (40%) had microscopic hematuria. There was no patient with macroscopic hematuria. Two of the patients had cardiac involvement and one had liver involvement. Serum C3 level was low in two patients. No monoclonal band was detected in serum in 5 patients. Monoclonal band was observed in serum protein electrophoresis and immunoelectrophoresis in 4 patients. Serum free light chain level was found to be high in 3 patients.

## Treatment and prognosis

In our study, we examined our patients diagnosed with MGRS who applied to my center. The most common subtype associated with monoclonal gammopathies is AL amyloidosis. The clinical presentation of approximately 75% of patients with AL amyloidosis, a subtype of MGRS, is edema and proteinuria. Plasma creatinine concentration is usually normal. ESRD develops in 20% of cases. There is no correlation between glomerular amyloid staining intensity and proteinuria in biopsies. Diffuse amorphous staining hyaline material is observed in light microscope examination. In immunofluorescence examination, lambda or kappa light chains are positively stained [14]. Although there is clonal proliferation of renal AL amyloidosis plasma cells, most patients do not develop multiple myeloma; Although light chain over production is present in most patients with multiple myeloma, renal amyloidosis does not develop [15]. International Kidney and Monoclonal Gammopathy Research Group suggested in 2012 to use the term monoclonal gammopathy (MGRS) with renal significance in such patients [7]. This term was suggested in the group of patients who did not meet criteria for multiple myeloma but had secondary renal damage due to M protein. Our patients did not meet the criteria for multiple myeloma by bone marrow examination and were diagnosed with MGRS by renal biopsy. In the study of Shaik et al., 6% of the patients followed up with the diagnosis of MGUS were diagnosed with MGRS [16]. In a study by Steiner et al., 2935 patients with a diagnosis of MGUS were examined and 1.5% of those diagnosed with MGRS [17]. In a study evaluating patients who started dialysis in the Netherlands in 2016, it was reported that 1.1 percent of patients were diagnosed with MGRS [18]. In a study examining patients with biopsy-proven AL amyloidosis, lambda light chain amyloidosis was observed 12 times more [19]. Renal involvement was observed 4 times more in lambda amyloidosis cases. In this study, it was observed that the amount of proteinuria was higher in patients with renal amyloidosis diagnosed with lambda amyloidosis. Our patients were also diagnosed with lambda amyloidosis and their proteinuria levels were at nephrotic level in line with the literature. In another study in which a patient diagnosed with MGRS with monoclonal gammopathy and renal disease was examined, the renal disease of approximately half of the patients was found to be associated with monoclonal gammopathy [20]. In patients with MGRS, treatment is based on the type of renal injury and the B cell clone that produces immunoglobulin. Eradication of

monoclonal proliferating plasma cells should be aimed in the treatment [22].

Ten of our patients were treated with bortezomib-based chemotherapy. One of the patients was given lenalidomide. Autologous bone marrow was additionally performed in two patients. The mean follow-up period was  $26 \pm 34$  months. Multiple myeloma developed in one patient at 19 months during follow-up. At the end of the follow-up, 2 patients died, 3 patients developed End-Stage Renal Disease (ESRD).

### Discussion

MGRS is a rare form of hematological disorder that causes kidney damage presenting with a wide range of pathological lesions. Amyloidosis is the most common form. Even with mild clinical findings, serum protein electrophoresis and immune electrophoresis should be performed in patients who present with abnormal findings in the urine and mildly elevated creatinine. In patients with monoclonal bands and multiple myeloma diagnosis excluded, a detailed renal evaluation for MGRS must be performed before MGUS is diagnosed. Early consideration of performing renal biopsy in such patients prevents delay in the diagnosis of MGRS, provides early treatment and close follow-up of renal reserve functions, thus slowing the progression to end-stage renal disease. Early diagnosis and close follow-up are important because renal survival of MGRS patients can be improved with early treatment. More clinical studies are needed on this subject.

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