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Successful Treatment of Monoclonal Gammopathy of Renal Significance With Bortezomib in the Setting of Post-Viral SARs-CoV-2 Infection: Case Report

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Introduction: Monoclonal Gammopathy of Renal Significance (MGRS) is an immunoglobulin proliferative disorder that leads to the destruction of the renal glomerular basement membrane and progression to end-stage renal disease. The pathogenesis of MGRS is similar to that of multiple myeloma and chronic lymphocytic lymphoma but lacks criteria for either disease. This inability to characterize the disease creates a gap in diagnostic and treatment recommendations. Recent studies and observations suggest that the pathogenesis of MGRS correlates with an acute inflammatory reaction as seen in post-viral SARS-CoV-2 (COVID-19) patients.

Case presentation: Here, we present a 61-year-old male with MGRS following a COVID-19 diagnosis with signs of acute kidney injury (AKI). The diagnosis was one of exclusion following kidney and bone marrow biopsy that showed four percent plasma cells and monoclonal protein IgG lambda light chains which did not meet the criteria for multiple myeloma. Historically the treatment of MGRS has targeted the underlying kidney pathology; however, evidence now supports treatment customization to the nature of the clonal M protein proliferation involved in the pathogenesis of the disease.

Conclusion: This case study demonstrates the novel finding of COVID-19-induced MGRS, which was successfully treated with dexamethasone and bortezomib to reduce the progression of kidney injury in MGRS.

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INTRODUCTION

Monoclonal Gammopathy of Renal Significance was initially proposed in 2012 to identify a group of disorders that meet the criteria for monoclonal gammopathy of undetermined significance (MGUS) and demonstrate features of advancing kidney disease [1]. The pathogenesis of the disease involves the proliferation and deposition of immunoglobulins along the glomerular basement membrane but lacks systemic findings of multiple myeloma, Waldenström macroglobulinemia, or symptomatic lymphocytic leukemia [2, 3]. Recent studies have proposed the effect of viral infections such as COVID-19 on the development of blood dyscrasias, but there has been little information citing the viral involvement in the development of a renal-directed process such as MGRS. COVID-19

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has been shown to initiate an excessive immune system response that can lead to a cytokine storm. A notable cytokine involved in this reaction is IL-6, which contributes to the differentiation of immunoglobulin-secreting plasma cells and maybe play a role in the pathogenesis of MGRS [4-7]. In addition to the potential role of COVID-19 in the development of MGRS, this case report provides evidence to support the successful treatment of MGRS using bortezomib and dexamethasone. Pathological immunoglobulins of this disease are targeted with specific drugs, but there has been a dispute as to whether this disease should be treated with chemotherapeutic agents [8]. The most current National Comprehensive Cancer Network (NCCN) guidelines indicate that targeted therapy such as the chemotherapeutic agent and glucocorticoid mentioned above are appropriate first-line treatment [9].

CASE PRESENTATION

A 61-year-old male with a past medical history of hypertension and hyperlipidemia presented to the emergency department with lower extremity edema on 1/16/2021 following a COVID-19 infection. He was hypertensive at the time of admission but denied any history of nephrotic-like symptoms such as edema or foamy urine. A doppler ultrasound was performed to exclude deep venous thrombosis, and the specific laboratory values are seen in Table 1. He was discharged home on furosemide and prednisone for suspected nephrotic syndrome. On 1/22/2021, the patient presented to his primary care provider with complaints of persistent lower extremity and periorbital edema, a blood pressure of ~180/100, and a weight gain of 20 pounds in 10 days.

The patient received a cardiac workup, and after a negative cardiac stress test, an echocardiogram revealed left atrial dilation. There was a possibility that the swelling was a side effect of his previous COVID-19 infection. His creatinine and GFR slightly worsened, which prompted a referral to nephrology. The patient continued to follow up with nephrology for proteinuria treatment with spironolactone and Olmesartan. The patient's GFR, BUN, creatinine, and frothy urine improved, but the protein concentrations and protein creatinine ratio had increased (Figure 2). We considered that proteinuria could result from long-standing hypertensive nephrosclerosis. A renal biopsy was performed on 6/8/2021 to evaluate for focal segmental glomerulosclerosis and primary nephropathies, which were processed according to standard practice (Figure 1)[7]. Routine frozen section immunofluorescence microscopy was positive for focal segmental deposits of C3 (3+) in mesangial areas with some extension into capillary loops. IgG and kappa light chains were positive (2+) in a peripheral granular pattern. Lambda light chains and IgM were negative. Electron microscopy demonstrated subendothelial deposits, endocapillary hypercellularity, and mesangial expansion with deposits. A diagnosis of Membranoproliferative Glomerulonephritis with Masked Monotypic Immunoglobulin Deposits on a renal biopsy was made [10].

The primary etiological differentials at that time included infectious, autoimmune, or plasma cell dyscrasia. An infectious etiology was less likely due to negative results for Histoplasma, Brucellosis, Tuberculosis, Hepatitis A, and Bartonella. His serum protein electrophoresis showed an immunofixation of a small IgG lambda monoclonal protein, which led to a referral to oncology on 6/18/2021. Oncology ordered labs including a skeletal survey, Kappa-Lambda light chains, immunoglobulins, and urine protein electrophoresis. The results returned negative, which essentially ruled out multiple myeloma. A bone marrow biopsy completed on 6/25/21 showed four percent plasma cells with a monoclonal protein IgG lambda similar to what was found on the renal biopsy. Prednisone 30mg was prescribed to prevent worsening renal function but still with an unclear diagnosis. On 7/21/21, the patient was referred to an academic medical center for the second opinion due to the rarity of MGRS. The academic medical center agreed that the

Table 1: Laboratory Values at Initial Presentation, January 2021

BUN (mg/dL)	GFR (mL/min/1.73 sq meters)	Creatinine (mg/dL)	BNP (pg/mL)	Protein/Creatinine Ratio, Urine	Total Urine Protein (mg/24hr)
31	55-59	1.25-1.33	283	6,140	8,869

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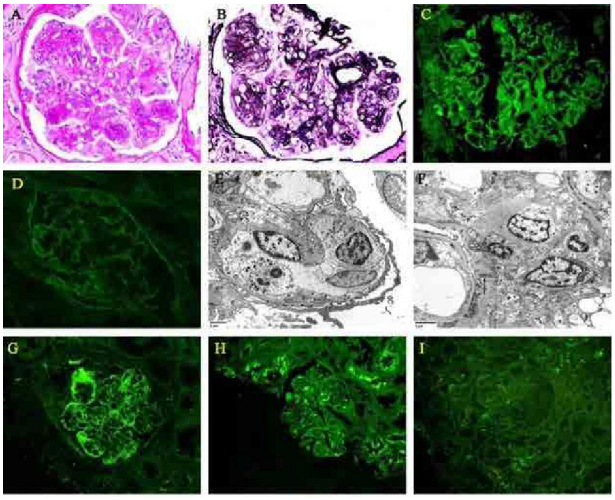


Figure 1: Renal Biopsy
Light, Immunofluorescence, and electron microscopy findings demonstrating mesangial proliferation and endocapillary changes. A) Mesangial expansion with endocapillary hypercellularity (periodic acid-Schiff reaction, original magnification 400x); B) Proliferative mesangial and endocapillary changes with new basement membrane formation forming double contours (Jones silver stain, original magnification 400x); C) Immunofluorescent stain for C3c with mesangial and capillary loop deposits (original magnification 400x); D) Immunofluorescent stain for IgG with no reaction (original magnification 400x); E) Electron photomicrograph showing endocapillary hypercellularity. New basement membrane formation and subendothelial deposits. (original magnification 4000x); F) Electron photomicrograph showing mesangial cell and matrix increase with occasional mesangial deposits (Arrow, original magnification 5000x); G) Immunofluorescent stain for IgG on FFPE sections showing mesangial and capillary loop deposits (original magnification 200x); H) Immunofluorescent stain for kappa light chains on FFPE sections showing mesangial and capillary loop deposits (original magnification 200x); I) Immunofluorescent stain for lambda light chains on FFPE sections with no reaction (original magnification 200x): FFPE: formalin-fixed, paraffin-embedded sections following antigen retrieval

workup and renal biopsy were consistent with MGRS. Therefore, 4-6 cycles of bortezomib and dexamethasone were administered along with acyclovir 400mg twice daily for herpes virus reactivation prophylaxis. The patient completed six cycles of chemotherapy on 2/10/2022 and has been doing well. As for the last follow-up in the clinic on 7/21/2022, the patient did not show frothy urine, kidney function was within normal limits, and his urine proteins (Figure 2) were improving. The patient only complains of fatigue with stable back pain but denies numbness or tingling. Oncology will continue to monitor his labs and symptoms.

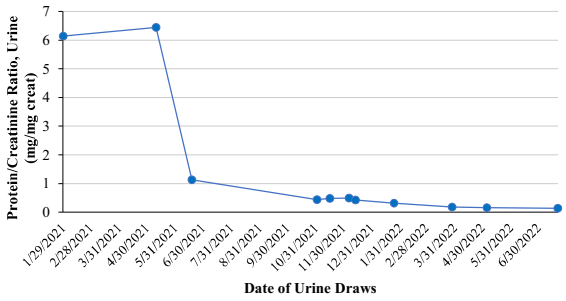


Figure 2: Urine Protein/Creatinine Ratio (mg/mg creatinine) Throughout the Patient's Treatment Course

DISCUSSION

MGRS describes any B-cell or plasma cell clonal lymphoproliferative disorder with a predisposition for the kidneys that do not create a tumor burden or meet the criteria for Multiple Myeloma, Walden Strom myeloma, or Chronic Lymphocytic Leukemia (CLL)[11]. MGRS produces immunoglobulins, classified as M proteins, that lead to renal glomerular, tubulointerstitial, and vascular lesions causing irreversible damage and the need for dialysis [10, 11]. The kidneys are often the most affected organ due to receiving the highest volume of cardiac output, renal environment's unique pH, and electrolyte concentrations that can alter the structure of M proteins [11]. The inability to classify these diseases as cancer has led to a gap that has interfered with treatment recommendations and created high morbidity secondary to severe renal lesions [8]. In considering a patient with MGRS, there are three diagnostic characteristics: failure of immunosuppressive regimens, high rate of recurrence post-transplant, and high risk of complications leading to worsening disease [1]. The risk of MGRS increases with age and can present with high urinary protein levels, high serum-free light-chain ratios, and microscopic hematuria [12]. According to the NCCN guidelines, if MGRS is suspected, eGFR, urinalysis, and metabolic testing are required for the initial workup. For an abnormal result, NCCN recommends a renal biopsy: the diagnosis is confirmed with immunofluorescence demonstrating monotypic immunoglobulin deposition [9]. Additional serum and urine studies can help to detect the presence of monoclonal immunoglobulins whose identity can be further evaluated via flow

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cytometry. Bone marrow biopsies can determine the origin of the lymphoproliferative clone [10]. Based on the hematologic results, further treatment options can target the monoclonal proteins.

Our patient had unique characteristic: the onset of MGRS was preceded by a COVID-19 infection. The COVID-19 virus has a widespread effect on the body by infecting the host via the ACE-2 inhibitor located throughout the body, including the kidneys. The mechanism behind this virus allows for the influx of inflammatory cells, renal vasoconstriction, and endothelial dysfunction: all of which can lead to increased IL-6 and cytokine storm. It suggests that increased cytokines can activate plasma cells to create a monoclonal gammopathy and precipitation to MGRS, as seen in this patient [13]. Medical intervention in the setting of MGRS is imperative due to the risk of end-stage renal disease (ESRD) that often recurs even the following transplantation [1]. The ESRD seen in Monoclonal Gammopathy of Renal Significance cannot be prevented through treatment with immunosuppressive agents or renin-angiotensin system inhibitors [11]. Current treatments for MGRS include Rituximab, Cyclophosphamide, Dexamethasone, and Bortezomib, with Bortezomib being the most successful [11]. There are multiple combinations for specific targets such as Rituximab in the gammopathies that are B-cell CD20 predominant, Dexamethasone for non-IgM monoclonal immunoglobulins, and the combination of Rituximab, Cyclophosphamide, and Dexamethasone for IgM monoclonal immunoglobulins [14]. Bortezomib has shown promise in delaying the progression of kidney disease in MGRS patients by inhibiting the chymotrypsin-like site of the 20S proteolytic core within the 26S proteasome to induce cell cycle arrest and apoptosis [15].

The combination of bortezomib, cyclophosphamide, and dexamethasone has been proved to be extremely effective with response rates as high as 94% [8, 15, 16]. If a patient with MGRS were to progress to ESRD, a kidney transplant would be the first line of treatment. Bortezomib can be recommended in the post-transplant setting to prevent post-transplant disease recurrence [10]. The primary limiting side effect of bortezomib was peripheral neuropathy, for which our patient suffered. In this report, the patient demonstrated MGRS with a correlating etiology of COVID-19 infection. The MGRS can be treated with the bortezomib and dexamethasone regimen if the side effects are tolerated. While this is promising for the future of MRGS treatment, there are still gaps in determining the optimal time for renal transplantation based on partial response rates. While the classifications of disease differ, monoclonal gammopathy of renal significance can have nephrotoxic outcomes similar to multiple myeloma and CLL. MGRS may be precipitated by COVID-19 infection; however, individuals affected can obtain successful remission. Studies have proposed that proliferation and pathogenesis of immunoglobulin-producing plasma cells increase throughout the COVID-19 disease course creating a potential trigger for MGRS. This suggests MGRS can be exacerbated in a post-viral setting secondary to cytokine production. It is unclear whether these processes are caused by COVID-19 infection or if COVID-19 merely has a role in accelerating the disease process. Regardless of the etiology of MGRS, bortezomib and dexamethasone remain successful treatment options in reducing morbidity. MGRS can lead to end-stage renal disease; however, early diagnosis and targeted treatment can prevent and potentially limit renal damage. Renal dysfunction and plasma dyscrasias are a part of the conflict of many organ systems that can be affected by COVID-19. As COVID-19 remains persistent in the global population, it is important to remain vigilant for long-standing side effects.

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CONFLICTS OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

Not applicable

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