

# Successful Renal Outcome in Membranoproliferative Glomerulonephritis Following Treatment of the Underlying Subtle Clone: A Case Report

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## Abstract

Membranoproliferative glomerulonephritis (MPGN) secondary to a monoclonal gammopathy is a rare glomerular disease and is defined as a monoclonal gammopathy of renal significance. The disease is characterized by glomerular monotypic immunoglobulin deposits and specific changes on light microscopy and electron microscopy. Immunochemistry is required to establish monoclonality, and electron microscopy helps to characterize the deposits ultrastructurally. Investigation for the underlying monoclonal protein should be done. We report a case of MPGN secondary to monoclonal gammopathy of renal significance that responded to treatment of the underlying clone with chemotherapy, resulting in improvement in renal function. Patients with MPGN and immunoglobulin deposition should be evaluated for a monoclonal protein to guide the management strategy.

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**M**onoclonal gammopathy of renal significance (MGRS) refers to low-grade plasma cell disorders that result in renal damage due to a nephrotoxic monoclonal paraprotein and in which the underlying clonal disorder does not meet the hematological criteria for specific treatment. Unlike monoclonal gammopathy of undetermined significance (MGUS), which is not associated with end-organ damage, MGRS causes renal damage that can have major clinical implications, including progression to end-stage renal failure (ESRF) and increased mortality risk.<sup>1-3</sup>

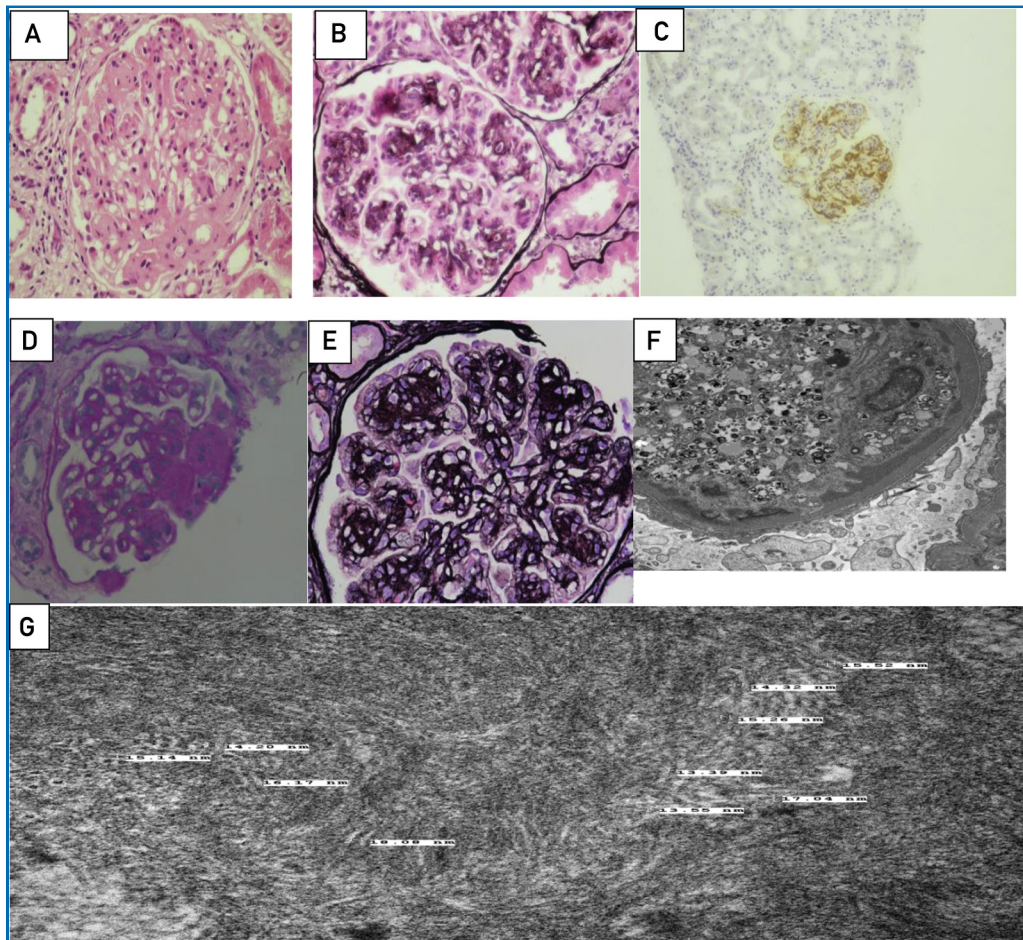
A range of renal lesions have been described with MGRS. The type of renal lesion depends on the physicochemical property of the involved monoclonal protein. The classification system can be based on the ultrastructural features of the deposits. In most patients, the deposits include or are a local product of clonal immunoglobulin. However, in C3 glomerulopathy, the

deposits are due to distal effects of the clonal immunoglobulin.<sup>4-10</sup>

There are 2 major types of membranoproliferative glomerulonephritis (MPGN), immune complex-mediated MPGN and complement-mediated MPGN. Immune complex-mediated MPGN has been classified into 3 groups: chronic infections, autoimmune diseases, and MGRS. Although MGRS-related MPGN does not classify as a true “immune complex” disease, it is being recognized as a separate entity, immune complex-mediated, and a cause in some cases of complement-mediated MPGN.<sup>8</sup>

In MGRS-related MPGN, there is an excess of a single type monoclonal immunoglobulin (MIg) or its components produced by an abnormal clone of a cell of B-cell lineage. The clonal immunoglobulin has a structural configuration that causes the histological changes of MPGN, through either MIg deposition or isolated complement deposition (C3 glomerulopathy).<sup>4-10</sup> The finding of this pattern of

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**FIGURE 1.** Pathology of membranoproliferative glomerulonephritis with monoclonal IgG deposits. A-C, First biopsy. A, Glomeruli exhibit diffuse accentuation of the nodular pattern, with mesangial matrix expansion (hematoxylin-eosin,  $\times 200$ ). B, Silver stain, showing thickening of the membranes with double contours and endocapillary proliferation. C, Immunohistochemistry highlights faint IgG in the peripheral capillary loops. D-G, Second biopsy. D, Hypercellular glomerulus with nodular mesangial expansion, endocapillary proliferation, thickening of glomerular basement membranes and double contours (hematoxylin-eosin,  $\times 200$ ). E, On silver staining, double contours of the GBMs and mesangial deposits are seen. F, Electron microscopy showing marked expansion of the mesangium with granular subendothelial deposits and moderate effacement of podocyte foot processes. G, Electron microscopy showing mesangial areas with a fibril deposition. GBM = glomerular basement membrane.

changes in a kidney biopsy necessitates evaluation for an underlying B-cell clone. Because the clonal immunoglobulin is usually low grade, careful serum and urine studies are needed to establish the presence of MGRS; occasionally, despite clear evidence of an MGRS-related MPGN on kidney biopsy, a serum and/or urine clonal immunoglobulin is not detected.<sup>11,12</sup>

Bone marrow biopsies performed in patients with MGRS-associated MPGN have revealed various conditions. Most commonly, a low-level

clone is reported, and previously this would have been described as MGUS.<sup>13,14</sup> Other known associated conditions are low-grade B-cell lymphoma, lymphoplasmacytic lymphoma, chronic lymphocytic leukemia, and multiple myeloma.<sup>14</sup> In some patients, there is no evidence of clonal plasma cell/B-cell lineage proliferation in the bone marrow, and the clone is being produced at an extramedullary site.

Although the pathogenesis of MGRS-related MPGN is now better understood,

evidence regarding renal outcome after the treatment of patients who have the underlying renal lesion is lacking. As renal outcomes are improved in other renal diseases that are associated with a clonal protein (eg, AL amyloid and Mlg deposition disease), due to targeting of the underlying cell clone,<sup>15-17</sup> there is strong justification for this approach in patients with MGRS-related MPGN. It is now accepted that when there is evidence of MGRS, treatment with plasma cell-based therapy is indicated.

Here, we report a case of MGRS-related MPGN that illustrates the challenges associated with the clinical management of this condition. Kidney function monitoring, serial kidney biopsies, and bone marrow biopsies showed disease progression; subsequent chemotherapy led to improvement in the burden of the clonal immunoglobulin and marked improvement in kidney function and proteinuria.

## REPORT OF CASE

A 66-year-old woman was referred to the nephrology clinic with hypertension and an active urinary sediment. She had previously been investigated for microscopic hematuria with normal findings on prior renal tract ultrasonography and cystoscopy. She had a history of myalgia, lower back pain, and occasional cramps. There was no history of weight loss, edema, arthritis, or rash. Her medical history included hypothyroidism, Bell palsy, and a neuro sarcoid that was not paraprotein related. She had no family history of kidney diseases. She was a nonsmoker and did not drink alcohol. She had 2 children with no history of preeclampsia.

Her blood pressure was 160/84 mm Hg, her weight was 82.1 kg, and her clinical examination results were normal. Urinalysis showed 3+ protein and 3+ blood. Albumin-creatinine ratio (ACR) was 268 mg/mmol; Modification of Diet in Renal Disease estimated glomerular filtration rate (eGFR) was 64 mL/min per 1.73 m<sup>2</sup>, albumin concentration was 36 g/L, calcium and alkaline phosphatase levels were normal, and hemoglobin value was 10.9 g/dL (to convert to g/L, multiply by 10.0) with normal hematinics.

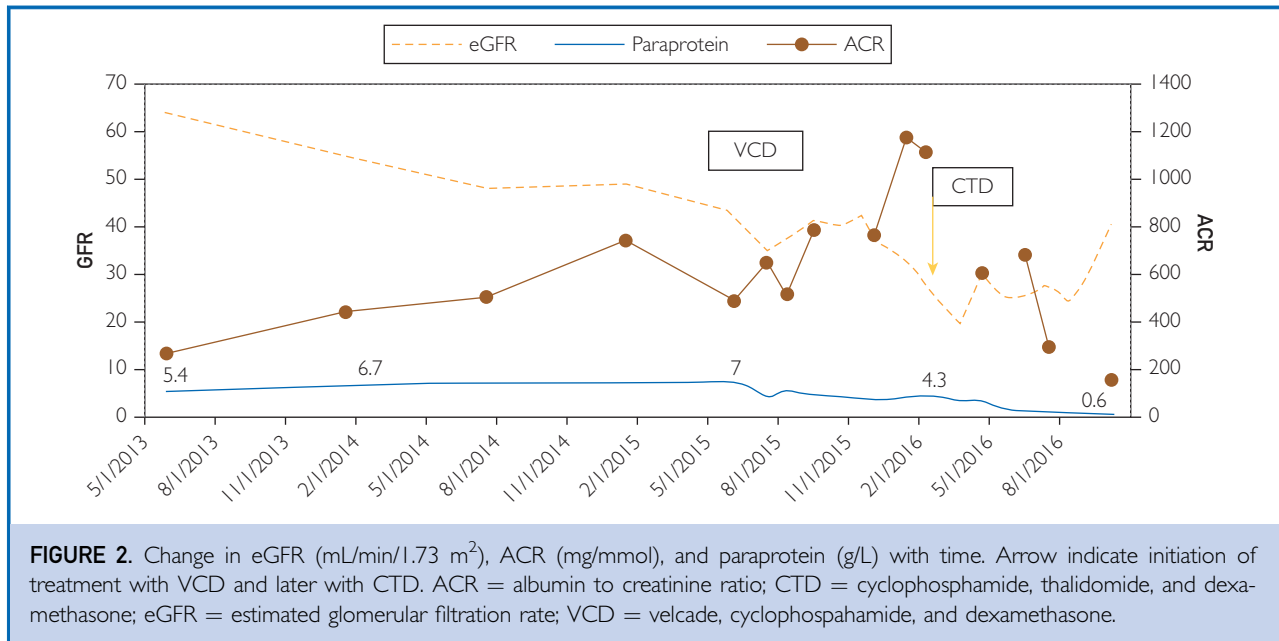
Serum protein electrophoresis showed an IgG lambda paraprotein on immunofixation, and clonal immunoglobulin quantitation was

5.40 g/L. Serum immunoglobulin levels were normal (IgG, 9.96 g/L; IgA, 1.49 g/L; IgM, 1.31g/L); serum free light chain results showed no evidence of free light chain clonality, with  $\kappa$  light chain of 26.30 mg/L,  $\lambda$  light chain of 23.55 mg/L, and a  $\kappa$ : $\lambda$  ratio of 1.1. Urine  $\kappa$  light chain level was 0.02 g/L, and urine  $\lambda$  light chain level was 0.01 g/L. Urine was negative for free light chains on immunofixation.

Immunology profile revealed a negative antineutrophil cytoplasmic antibodies level, and antinuclear antibodies titer was 1:10 (homogeneous pattern) with a negative double-stranded DNA. Complement levels (C3 and C4) were normal. Serology was negative for hepatitis B and C.

She underwent a renal biopsy that showed type 1 membranoproliferative glomerulonephritis (Figure 1, A-C). There was diffuse accentuation of the nodular pattern, associated with mesangial matrix expansion. Double contours were evident on silver staining, and there was focal endocapillary proliferation. On immunostaining, there was faint IgG and strong diffuse C3d along the peripheral capillary loops. Electron microscopy showed marked expansion in the mesangial matrix, which demonstrated a filamentous appearance. There were no mesangial and no subepithelial deposits but several capillary loops contained scattered subendothelial deposits. Marked effacement of the foot processes was noted. There were no casts and Congo red stain was negative.

Further investigations showed a small rise in IgG lambda paraprotein quantitation at 7.2 g/L. Skeletal survey was negative and bone marrow biopsy showed a clonal population of plasma cells with a skewed  $\kappa$ : $\lambda$  ratio of 1:5; these cells were CD117, cyclin D1, CD20-negative, and CD56-positive, accounting for 2% to 3% of the total nucleated cell count. She had a full-body computed tomography scan that demonstrated small-volume adenopathy both above and below the diaphragm; this was felt to be long-standing and related to her history of sarcoid. She was diagnosed with MGUS, and given the uncertainty as to whether there was a direct connection with her renal disease, a period of monitoring was felt to be appropriate to determine whether there was a need for treatment.



**FIGURE 2.** Change in eGFR (mL/min/1.73 m<sup>2</sup>), ACR (mg/mmol), and paraprotein (g/L) with time. Arrow indicate initiation of treatment with VCD and later with CTD. ACR = albumin to creatinine ratio; CTD = cyclophosphamide, thalidomide, and dexamethasone; eGFR = estimated glomerular filtration rate; VCD = velcade, cyclophosphamide, and dexamethasone.

Over the next 2 years, her proteinuria worsened (ACR, 268 mg/mmol to 741 mg/mmol) and she developed nephrotic syndrome (albumin, 30 g/L). Discussion between her treating nephrologist and hematologist resulted in repeated staging of her plasma cell dyscrasia. A further bone marrow biopsy showed an increase in clonal plasma cells to 10% with  $\lambda$  light chain restriction, consistent with plasma cell myeloma. Her M-protein level over this period increased from 5.4 g/L to 7.1 g/L, and there was a 20% decline in her eGFR (64 mL/min to 51 mL/min) (Figure 2).

She received 4.5 cycles of attenuated bortezomib, cyclophosphamide, and dexamethasone chemotherapy. Her treatment was complicated by fluid retention and macroscopic hematuria from cyclophosphamide, requiring mesna. A repeated flexible cystoscopy did not reveal any abnormality. The patient initially had a partial response to chemotherapy; the paraprotein level fell from 7.1 g/L to 3.5 g/L and subsequently plateaued (Figure 2).

Despite a partial hematological response, her renal function and proteinuria continued to deteriorate (eGFR, 64 mL/min to 42 mL/min; ACR, 268 mg/mmol to 769 mg/mmol; Figure 2). A repeated renal biopsy was performed to assess for evidence of renal disease progression; this again showed a membranoproliferative pattern (Figure 1, D-G) but there was

more chronic damage, and an increase in extravasation of Tamm-Horsfall protein. This was proposed as a substantial contributing factor to the degree of chronic damage, and a proposed mechanism for the increase in proteinuria. On immunostaining, there was peripheral capillary loop staining with IgG and with C3d and C1q. On electron microscopy, there was marked mesangial expansion with granular subendothelial deposition and moderate effacement of podocyte foot processes. The renal biopsy taken 2 years previously was reviewed again with light chain immunostaining. There appeared to be preferential  $\lambda$  staining of the membranous deposits with negative  $\kappa$  staining.

Because the renal biopsy was consistent with ongoing active MIg deposition, it was decided to target the clone further with a thalidomide-based regimen, to aim for a deeper clonal response.

She received 6 cycles of attenuated cyclophosphamide, thalidomide, and dexamethasone and her paraprotein fell to 0.6 g/dL (Figure 2). After second-line treatment, the renal parameters improved (ACR, 1115.8 mg/mmol to 154 mg/mmol; eGFR, 19 mL/min to 47 mL/min), resulting in a favorable renal outcome (Figure 2).

She has completed 2 years of joint renal and hematology follow-up since completing chemotherapy, and her current eGFR is 54 mL/min per 1.73 m<sup>2</sup> and ACR 25 mg/mmol.

## DISCUSSION

The MGRS-related MPGN is rare.<sup>18</sup> This disease is characterized by glomerular nonorganized, granular, monotypic immunoglobulin deposits (commonly IgG3k), without any deposits along the tubular basement membrane.<sup>11</sup>

The disease pathogenesis is not well understood. One theory is that the MIg rapidly deposits in glomeruli through entrapment and/or interaction with the negatively charged glomerular constituents, to form definable electron-dense deposits.<sup>11</sup> Other theories suggest the secretion of various biological factors or autoantibody activity of MIg.<sup>19</sup>

Diagnosis requires a renal biopsy, screening for a monoclonal protein, and a complete hematological work-up. Monoclonality in the renal biopsy can be determined by immunofluorescence, thereby providing clues to the underlying pathophysiology. It is very important to correlate the specific MIg found on biopsy with that found during the hematologic work-up to ensure a direct link is established between the MIg and type of nephropathy.<sup>20</sup>

The diagnosis of this condition is often challenging, because it has been reported that many patients do not have an identifiable peripheral clone.<sup>20</sup> Serum and urine MIg has been reported to be found in only one-third of patients, and a monoclonal proliferation of plasma cells in the bone marrow is found in less than 10% of patients.<sup>15,18,21,22</sup>

The term MGRS defines a group of conditions with a wide variety of histological findings on renal biopsy. The clinical features and disease phenotype are broad and dependent on the underlying condition. The term MGRS enables clinicians to distinguish monoclonal gammopathies that result in development of kidney disease from those that do not, and are not associated with conventional indications for chemotherapy.<sup>15</sup> Because MGRS-related MPGN is so rare, the literature surrounding renal outcome is very limited. There are, however, studies of other conditions within the MGRS group that have looked at renal outcomes. A study of 56 patients with monoclonal immunoglobulin deposition disease (MIDD) reported that most patients (63%) who did not receive treatment progressed to ESRF. In 32 patients treated with chemotherapy, 11 (34%) progressed to ESRF.<sup>23</sup> These results highlight the importance of an early diagnosis to enable

treatment, to preserve and potentially restore kidney function.

A study at the UK National Amyloid Centre, in patients with light chain deposition disease, reported that patients who achieved a complete or very good partial hematological response with chemotherapy had a mean improvement of 6.1 mL/min per year in glomerular filtration rate compared with a mean glomerular filtration rate loss of 6.5 mL/min per year in patients with partial or no response.<sup>24</sup> Factors predictive of a renal response in MIDD are pretreatment eGFR more than 30 mL/min per 1.73 m<sup>2</sup> and posttreatment difference in the involved and noninvolved free light chain level less than 40 mg/L.<sup>16</sup> Although MIDD and light chain deposition disease confer a different disease phenotype, these studies add weight to the conclusion that the goal of therapy in other forms of MGRS, such as MGRS-related MPGN, should be to target a deep clonal response.

Because of the rare nature of this disease, there is no standard treatment strategy for patients with MGRS-related MPGN. Various treatment regimens including immunosuppressive regimens have been reported in the literature with variable outcomes.<sup>14,20,21</sup> Clone-directed treatment is recommended as first-line treatment in MGRS, and specific therapy targeting B-cell and plasma-cell clones can be added on the basis of severity of kidney disease and clinical judgment.<sup>12</sup> The requirement for treatment with chemotherapy needs to be carefully balanced against the potential risks associated with chemotherapy. Because MGRS is a rare entity, collaborative efforts of both nephrologists and hematologists are required to guide management.

Here, we report a case of MGRS with a subtle underlying clone that progressed to multiple myeloma over time. Achievement of a near-complete clonal response was required before any renal response occurred. Our patient showed improvement in both renal function and proteinuria after successful suppression of the underlying clone. The degree of improvement in both renal function and proteinuria would suggest that the increase in chronic damage was not the main driver for the increase in proteinuria over time and highlights that there is scope for improvement despite significant chronic changes. Further studies are required to define

whether treatment has an impact on survival in this rare disease.

**Abbreviations and Acronyms:** **ACR** = albumin to creatinine ratio; **eGFR** = estimated glomerular filtration rate; **ESRF** = end-stage renal failure; **MGRS** = monoclonal gammopathy of renal significance; **MGUS** = monoclonal gammopathy of undetermined significance; **MIDD** = monoclonal immunoglobulin deposition disease; **Mlg** = monoclonal immunoglobulin; **MPGN** = membranoproliferative glomerulonephritis

**Potential Competing Interests:** Dr Drayson is a medical advisor to and shareholder in Abingdon Health, which is an immunodiagnostics company. The rest of the authors report no competing financial interests.

**Publication dates:** Received for publication March 8, 2018; revisions received April 23, 2018; accepted for publication April 24, 2018.

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