A Patient with Abnormal Kidney Function and a Monoclonal Light Chain in the Urine

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Abstract
Monoclonal gammopathy is increasingly recognized as a cause of kidney injury. These renal conditions behave differently than ones without monoclonal gammopathy and require specific treatment. To avoid misdiagnosis, testing for paraprotein should be performed in addition to vasculitis and autoimmune diseases serologies in adults with unexplained AKI or proteinuria. Because the prevalence of monoclonal gammopathy is much more common than glomerular diseases, the nephrotoxicity of the monoclonal protein must be confirmed before cytotoxic therapy is initiated. This can only be done by a kidney biopsy. After a monoclonal gammopathy of renal significance is verified, the evaluation should then focus on the identification of the pathologic clone, because therapy is clone specific. We present this patient to illustrate the clinical presentation of a patient with renal dysfunction and a monoclonal gammopathy. This patient is also used to discuss the diagnostic process in detail when monoclonal gammopathy–associated renal disease is suspected.


Introduction
A 56-year-old man presented for a second opinion on his recently diagnosed kidney disease. The patient was healthy until several months earlier, when he developed sudden onset of severe hypertension that was poorly controlled, despite nebivolol, doxazosin, hydrochlorothiazide, and furosemide. Severe lower extremity edema developed after initiation of amiodipine. Proteinuria was later found, leading to a kidney biopsy, which was reported as membranoproliferative GN type 1. Serologies to hepatitis and antinuclear antibodies were negative. C3 was slightly decreased at 69 mg/dl (normal range = 75–175 mg/dl), whereas C4 was normal at 27 mg/dl (normal =14–40 mg/dl). Lisinopril was started for the proteinuria, but no immunosuppression was given.

At our institution, he had a creatinine of 2.7 mg/dl (normal =0.8–1.3 mg/dl) and a hemoglobin of 10.2 g/dl (normal =13.5–17.5 g/dl). Urinalysis showed nondysmorphic hematuria with 11–20 red blood cells/hpf, hyaline casts, granular casts, and nephrotic sediment. Proteinuria was measured at 7.4 g/dl, with a serum albumin of 2.0 g/dl (normal =3.4–4.7 g/dl). Serum and urine protein electrophoresis (PEP) were negative for any monoclonal protein. Urinary albumin was 58%. On immunofixation (IFE), a monoclonal κ–light chain was identified in the serum and urine. Serum free light–chain (sFLC) assay showed a κ–free light chain (κ-FLC) of 44.6 mg/dl (normal =0.33–1.94 mg/dl), λ of 3.38 mg/dl (0.57–2.63 mg/dl), and a ratio of 13.2 (normal =0.26–1.65). Total IgG was decreased at 230 mg/dl (normal =767–1350 mg/dl).

The Role of Monoclonal Proteins in Kidney Diseases
Monoclonal gammopathy (MG) is a significant cause of kidney diseases. The most recognized example of this is light–chain cast nephropathy, which occurs most commonly in symptomatic multiple myeloma (MM) (1). However, the notion that a malignancy, such as MM or lymphoma, is necessary for the development of kidney disease is no longer valid. Many kidney lesions are, in fact, associated with low–grade plasma cell dyscrasia or lymphoproliferative disorders rather than their malignant counterpart (2). In a large study of patients with Ig light–chain (AL) amyloidosis, 40% were found to have >10% plasma cells in the marrow, but only 8% had evidence of MM (3). Similarly, 59% of 63 patients with monoclonal Ig deposition disease (MIDD) were reported to have myeloma in a large Italian series (4). In a different study, where the bone marrow plasma cells and end organ damage were assessed separately, again, 59% were found to have >10% plasma cells in the bone marrow, but only 20% had lytic lesions at the time of diagnosis (5). This correlated with a recent French series showing that only 20% met the definition of MM (6). Other conditions that have low rates of MM include light–chain Fanconi syndrome, which occurs in only 31% of patients (7). Rates are even lower in immunotactoid GN (>5%) and proliferative GN with monoclonal Ig deposits (PGNMID; 2%) and extremely low in monoclonal fibrillary GN (<1%) (8–11). The presence of MM is not required for kidney disease, but when present, it does worsen the prognosis (12,13).

The lack of MM creates a problem, because treatment is only recommended for patients with MM (14). Currently, MM is defined by hypercalcemia, renal impairment, anemia, and bone lesions, which indicates end organ damage. The criteria were updated in 2014 to include three conditions (involved-to-uninvolved FLC ratio >100, bone marrow plasma cells >60%, and more than one bone lesion on magnetic resonance imaging) that have a high risk of progression to hypercalcemia, renal impairment, anemia, and bone lesions within 24
months. Patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are recommended not to undergo treatment, except in the setting of a clinical trial. This is made even more difficult since renal impairment unrelated to cast nephropathy is not considered a myeloma-defining event, because these conditions do not require the tumor burden seen in MM. To capture these as clinically significant hematologic conditions, the term monoclonal gammopathy of renal significance (MGRS) was introduced (15). Although hematologically, MGRS behaves more similar to MGUS and SMM, it differentiates itself by its nephrotoxicity. MGUS and SMM cannot have end organ damage by definition.

Regardless of the source of the monoclonal protein (MM, lymphoma, or MGRS clones), the monoclonal protein can produce a number of different renal lesions. The types of kidney injury seem to be determined mainly by innate characteristics of the monoclonal protein (16). One method of classifying these conditions is on the basis of the location of the injury. For example, in the glomerulus, MG can induce immunoglobulin derived (Alg) amyloidosis that includes AL amyloidosis, heavy-chain amyloidosis, and light- and heavy-chain amyloidosis (17). Other glomerular entities include MIDD, which is comprised of the variants light–chain deposition disease (LCDD), heavy–chain deposition disease, and light– and heavy–chain deposition disease named for the types of Ig deposits found in the kidney, and proliferative glomerulonephritidities, such as membranoproliferative GN (MPGN) and PGN MID (5,11). In the tubules, light–chain proximal tubulopathy (LCP T) with or without Fanconi syndrome and cast nephropathy are conditions associated with MG (18). Rare cases of diabetes insipidus have been reported with AL amyloidosis that have deposited in the distal tubules (19). Monoclonal light chains are also capable of generating hydrogen peroxides, which activates the mitogen–activated protein kinase kinase kinase, known as apoptosis signal regulating kinase 1, causing apoptosis and NFκB–light–chain enhancer of activated B cells (NFκB) via Src kinase resulting in fibrosis (20). Vascular involvement is common with amyloidosis and MIDD (5,21). The one issue with this classification is that overlap is common. The overlap can occur where multiple sites are involved, such as in Alg amyloidosis (glomerulus, tubules, and vessels), or more than one histology can be seen in a single kidney. In one study of 190 patients with MM and kidney biopsy, 12 (6%) patients had two paraprotein-related lesions, including cast nephropathy and MIDD, cast nephropathy and Alg amyloidosis, and MIDD and Alg amyloidosis (22). There are also patients with cast nephropathy with LCPT who have been described. In a rare incidence, cast nephropathy has been seen to coexist with both AL amyloidosis and LCDD in the same kidney (23,24).

Another method of classifying these conditions is by the ultrastructural characteristics of the deposits (Figure 1). The deposits are first categorized as organized versus nonorganized (25). The organized deposits are further classified as fibrils (Alg amyloidosis or monoclonal fibrillary GN), microtubules (immunotactoid GN or cryoglobulinemia), or crystals/inclusions (LCPT, crystal-storing histiocytosis, and cryocryoglobulinemia) (26–28). Light-chain casts occasionally have a crystalline structure that fractures during processing of the tissue. The entities that have nonorganized deposits are MIDD (Randall type), PG N MID, and C3 glomerulopathy (including C3GN and dense deposit disease, which have dominant C3 deposits) with MG (29–31). Of note, recent studies found that about one third of patients with C3GN have C3GN associated with an MG (31). Although the Ig is not well seen on standard immunofluorescence performed on frozen tissue, the Ig can be unmasked by pronase digestion of the paraffin-embedded tissue (32). Finally, a membranoproliferative-like lesion with mesangiolysis and microaneurysm suggestive of microangiopathy have been reported in patients with POEMS syndrome characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (33,34). Although these lesions are reminiscent of thrombotic microangiopathy, there is no evidence of ongoing microangiopathic hemolytic anemia (35). The glomerular changes are thought to be secondary to cytokines (IL-6 and vascular endothelial growth factor) activation by the A–restricted monoclonal proteins.

It is important to recognize that MGRS can also mimic kidney diseases normally not associated with MG. This occurs when the monoclonal protein targets the same antigens as the polyclonal Igs in the non-MGRS disease. A case of anti-gamma light–chain–related monoclonal basement membrane (anti–GBM) disease was reported with a monoclonal IgAκ targeting the α1/α2-chains of type IV collagen in a patient who presented with pulmonary renal syndrome with negative anti–GBM titers (36). The anti–GBM test was negative, because the Ig was an IgA and not IgG, which is what the test was designed to detect. A patient with recurrent membranous nephropathy in the renal allograft caused by a circulating monoclonal protein targeting the phospholipase A2 receptor has also been reported (37).

### Clinical Significance of MGs in Kidney Diseases

MGRS-associated nephropathies behave differently, even when they mimic renal diseases without MGRS. In idiopathic membranous nephropathy, approximately one third of patients undergo spontaneous remission (38). In anti–GBM disease, the overwhelming majority of patients have a monophasic course that does not recur after treatment (39). However, MGRS-associated nephropathies are progressive and recur frequently, even after kidney transplantation. This is because of the nature of low–grade lymphoproliferative disorders, which generally do not undergo spontaneous remission or remain in remission with conventional immunosuppression. Although the speed of recurrence differs, the high recurrence rate is similar among the different MGRS–associated nephropathies. In patients with PGN MID, recurrence can occur in as little as 3 months postkidney transplant (40,41). The median time to recurrence is 33 months in LCDD and even longer in AL amyloidosis (42). The recurrence rate, however, is 60%–80% in patients with a MG at the time of kidney transplantation for MIDD, membranoproliferative GN, and fibrillary GN (42–44). Risk of recurrence can be decreased if the patient achieves a hematologic complete response before kidney transplant. In a study of MGRS–related fibrillary GN, only patients with MG at the time of transplant had a recurrence (43). Another study of a patient with AL amyloidosis showed that recurrence was significantly reduced if the patient achieved a complete response with or without high-dose therapy followed by autologous stem cell transplantation (45).
How Are MGRS-Associated Nephropathies Diagnosed?

The most important diagnostic test for MGRS-associated nephropathies is the kidney biopsy (25). In fact, MGRS cannot be established without a kidney biopsy. This is essential, because the prevalence of MG is significantly higher than the incidence of glomerular disease (46–48). Thus, the nephrotoxicity of the monoclonal protein must be confirmed before initiating treatment (49). Identification of the monoclonal protein in the kidney is currently the only method that can link the monoclonal protein to the nephrotoxicity. The Ig deposits should be restricted to a single LC. The evidence for monoclonality is improved when there is a restriction to a single heavy–chain subtype (e.g., k IgG3) (25). In patients with C3GN, paraffin immunofluorescence after protease digestion is strongly recommended to look for masked Igs (32). If negative, serum should be tested for C3 nephritic factor (C3nef) and C4 nephritic factor, which are autoantibodies that protect the alternative pathway C3 convertase C3bBb (C3nef) or the classic C3 convertase C4b2a (C4 nephritic factor), causing persistent activation of the complement system (50). The alternative pathway could also be activated by monoclonal proteins acting as autoantibodies against complement inhibitors, such as factor H (29,31). Evaluation for genetic defects in the complement system should also be considered.

If the monoclonal protein testing was not performed before the kidney biopsy, it should be performed (15,25,49). From a diagnostic standpoint, this is important to link the kidney disease to the clonal proliferative disorder. This is vital when a biclonal gammopathy is present. In some patients, two separate clones may be responsible for the biclonal gammopathy. The identification of the pathologic MG will help direct therapy to the right clone. The monoclonal protein is also necessary as a marker of hematologic response after therapy. Renal response on the basis of proteinuria and creatinine reduction correlates with hematologic response (51–54).

Monoclonal Protein Assays

A number of tests is available for the detection of monoclonal proteins. The most common is PEP (55). PEP in commercial laboratories is automated and can be performed on both serum and urine at a relatively low cost and a high throughput. However, PEP is the least sensitive of the monoclonal protein tests, with a lower limit of detection at approximately 0.3 g/dl (56,57). This may be acceptable in high-tumor burden diseases, like MM, but is inadequate in low-burden diseases, like MGRS. The sensitivity of serum PEP is 87.6% in patients with MM but drops to 65.9% in AL amyloidosis, 55.6% in LCDD, and 15% in PGNMID (Table 1) (8). Urine PEP is generally much less sensitive than serum PEP but may be more specific for nephrotoxic FLCs (58). Sensitivity and specificity can be improved by performing IFE, which uses antisera to different Ig components to identify the monoclonal protein (57). IFE can be performed on both serum and urine. The detection limit for IFE is down to 0.1 g/dl. With serum IFE, 94.4% of patients with MM and 73.8% of patients with AL amyloidosis would be identified (56,57). The higher sensitivity and specificity do come with a higher cost. In addition, although IFE is able to determine the type of monoclonal protein, which PEP cannot, it does not quantify the protein like PEP. This means that IFE cannot be performed as a standalone test.

The most sensitive commercially available monoclonal protein test is the sFLC assay (56). The sFLC assay quantifies
the excess (free) light chains in circulation, and clonality is assumed when there is an excess of one sFLC over the other. A normal range is established for each FLC as well as the ratio between κ- and λ-FLCs in the serum. A high ratio suggests a κ-clone, whereas a low ratio indicates a λ-clone. The lower limit of detection is approximately 0.1 mg/dl, which is 1000-fold more sensitive than IFE. However, because sFLC assay does not distinguish between monoclonal versus polyclonal expansion, monoclonoality can be difficult to establish with small elevations in the sFLC concentration. In addition, nonmonoclonal processes can alter the concentrations of sFLCs. The most common example of this is renal impairment. In normal subjects, elimination of FLCs occurs predominantly via glomerular filtration. Normally, more κ-FLCs are filtered than λ-FLCs, because λ-FLCs exist in a dimeric state, which has a higher molecular weight. In the presence of renal impairment, the drop in GFR affects the elimination of κ-FLCs more than λ-FLCs, resulting in a higher κ-to-λ ratio. As a result, a renal range has been established for patients with severe renal impairment, where the upper limit of the κ-to-λ ratio is raised from 1.65 to 3.10 (59). Unfortunately, a normal range has not been established for each stage of CKD. Other nonclonal causes of FLC elevations are autoimmune diseases and infections. Assays for urinary FLC are commercially available. Unfortunately, the high variation from individual to individual and the lack of advantage over sFLC make the test difficult to interpret and unnecessary (60,61).

### Diagnostic Approach for Patients with Kidney Disease and an MG

The most important role of the nephrologist is to determine whether the monoclonal protein is involved in the renal disease. This can be difficult, because 5% of men and 3% of women age >70 years old will have an AMG, whereas the rate of kidney disease is only 1–2 per 100,000 per year (47,62). Another study found that only 36.8% of patients with MG who underwent a kidney biopsy had a paraprotein–related kidney disease (48). This means that most people with an AMG likely have MGUS rather than MGRS. In most patients, this can only be determined by a renal biopsy. There are two exceptions. One is light-chain Fanconi syndrome, where the presence of amino aciduria, normoglycemic glycosuria, hypophosphatemia, hypouricemia, and hypokalemia along with renal impairment and subnephrotic-range proteinuria are diagnostic (18). The other is AL amyloidosis, where the diagnosis can be established by nephotic-range proteinuria and amyloid found in nonrenal tissue (54). Unfortunately, not all patients with light-chain Fanconi syndrome have electrolyte abnormalities, especially when renal function is reduced, and patients with vascular-limited amyloidosis have low-grade or no proteinuria (63). Kidney biopsy remains necessary in these patients.

Although the laboratory generally cannot establish the diagnosis of MGRS or myeloma–related kidney diseases, two tests are quite useful in narrowing the differential diagnoses. The first is the FLC assay. Unlike the MGRS–associated nephropathies, cast nephropathy nearly always occurs in patients with MM, and in fact, it is a myeloma–defining event (14,64,65). The concentration of FLC must be sufficiently high to cause the tubular obstruction in cast nephropathy. Therefore, alternative diagnosis should be considered in patients with FLC levels of <50 mg/dl (64). A low or normal FLC concentration does not rule out MGRS–associated kidney diseases, because some can occur in very low clonal burden. Urine PEP is the other test that can also be useful in predicting the renal lesion. Data from patients who were enrolled in the Medical Research Council IV, V, VI, and VIII Trials in the United Kingdom showed that renal impairment was present in only 2% of patients without urinary Bence Jones protein excretion but ≤54% of those with high levels of urinary FLC excretion (58). Similar studies, however, have not been performed on other MGRS–associated nephropathies. In addition, the pattern of the urine PEP can be quite informative. Because cast nephropathy involves only the tubules, albuminuria should be low. This was, indeed, the result of a study with biopsy–proven renal lesions. In patients with cast nephropathy, the urinary albumin excretion was <10%, whereas it was 55% in MIDD and 70% in AL amyloidosis (66). Acute tubular necrosis fell in between, with some overlap with cast nephropathy and MIDD at 25%.

The monoclonal protein testing depends on the purpose of the assay. If the testing was performed to screen for an MG, regardless of kidney disease, then the most efficient testing would include serum IFE and sFLC. This would pick up all of the MM and MIDD and >95% of AL amyloidosis. However, this is different if the testing was performed in a patient who has a kidney disease, and an MG screening is done to determine if MGRS is present. In this patient, serum SPEP and urine IFE with total protein should be included as well to provide additional information. Finally, if a diagnosis of an MGRS–associated kidney disease is already made by kidney biopsy, both serum and urine tests are required for diagnosis and response assessment after treatment.

### Table 1. Performance characteristics of monoclonal protein tests

<table>
<thead>
<tr>
<th>Test</th>
<th>MM, %</th>
<th>AL, %</th>
<th>MIDD, %</th>
<th>PGNMID, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPEP</td>
<td>87.6</td>
<td>65.9</td>
<td>55.6</td>
<td>15</td>
</tr>
<tr>
<td>SIFE</td>
<td>94.4</td>
<td>73.8</td>
<td>55–73</td>
<td>20</td>
</tr>
<tr>
<td>sFLC</td>
<td>96.8</td>
<td>88.3</td>
<td>78–100</td>
<td>21</td>
</tr>
<tr>
<td>SIFE + UIFE</td>
<td>98.7</td>
<td>94.2</td>
<td>78–81</td>
<td>22</td>
</tr>
<tr>
<td>SIFE + sFLC</td>
<td>100</td>
<td>97.1</td>
<td>78–100</td>
<td>32</td>
</tr>
</tbody>
</table>

MM, multiple myeloma; AL, Ig light chain; MIDD, monoclonal Ig deposition disease; PGNMID, proliferative GN with monoclonal Ig deposits; SPEP, serum protein electrophoresis; SIFE, serum immunofixation; sFLC, serum free light chain; UIFE, urine immunofixation.
Back to Our Patient

A kidney biopsy was repeated. The glomeruli appeared enlarged and exhibited marked nodular mesangial expansion. The mesangial nodules were composed of silver–positive matrix material as well as silver–negative glassy immune deposits that stain weakly red on trichrome stain and were periodic acid–Schiff positive (Figure 2). Moderate global mesangial hypercellularity was also evident. GBMs were moderately and diffusely thickened with segmental duplication (Figure 2). No glomeruli with crescents or necrosis were seen. Mild tubular atrophy and interstitial fibrosis involving 5%–10% of the cortex were present. Mild arteriolosclerosis was appreciated. Immunofluorescence showed diffuse linear glomerular capillary wall, smudgy mesangial, linear tubular basement membrane, and vascular wall positivity for IgG (Figure 3). IgA, fibrinogen, k, and l were all negative (Figure 3). Glomeruli also showed 3+ smudgy mesangial positivity for C3 with 2+ C1q and 1+ IgM. Staining for IgG subtype showed that the glomerular deposits stained 3+ for IgG1 (Figure 3), negative for IgG2 and IgG3, and trace for IgG4. Nodular mesangial expansion by mesangial hypercellularity and deposition of massive punctate powdery electron dense deposits were seen on electron microscopy (Figure 4). Similar deposits were seen segmentally along GBMs (Figure 4). Podocytes displayed marked (80%) foot process effacement. The pathologic diagnosis was γ-heavy-chain deposition disease. A small κ-light chain–restricted plasma cells clone involving 5% of the cellular marrow was identified on bone marrow biopsy.

Our patient was successfully treated with a combination of cyclophosphamide, bortezomib, and dexamethasone. He achieved a complete hematologic response. After 5 years, creatinine improved to 1.2 mg/dl, and proteinuria normalized at 140 mg/dl. BP was well controlled on the single agent lisinopril. Treatment was complicated by mild peripheral neuropathy, which is well controlled with gabapentin.

Management of MGRS-Associated Nephropathies

When a kidney disease develops as a result of a malignancy, such as MM, lymphoma, or chronic lymphocytic leukemia, treatment should be directed toward the underlying malignancy on the basis of the latest data–driven treatment options. Similarly, in MGRS-associated nephropathy, the treatment must be directed toward the pathologic clone. Clones capable of producing monoclonal proteins include B cells, which are CD20+; B cells with plasmacytic differentiation (Waldenstrom), which carry the MYD88 mutation; CD5 and CD23 coexpressing B cells that are capable of developing into monoclonal B cell lymphocytosis, a precursor state to chronic lymphocytic leukemia (CLL); small lymphocytic lymphoma/CLL cells; and finally, plasma cells, which are typically CD20−, CD38+, and CD138+ (67–69). Treatment needs to be tailored toward each clone (49). In general, rituximab can be used against the CD20-expressing clones but would have little effect against plasma cells and only partial effectiveness against CLL (70). For these other clones, the addition of alkylator, proteosome inhibitors, immunomodulatory drugs, mAb against other cellular targets, or specific kinase inhibitors, such as Bruton tyrosine kinase inhibitor, may be necessary (71,72). Autologous stem cell transplantation, although not curative, may offer patients with deeper response and prolonged remission as well as extended coverage of multiple clones (52,73–75). However, toxicity is also much higher with autologous stem cell transplantation.

For many of the patients with MGRS, the hematologic condition is a low–grade clonal disease that poses no immediate danger to the patient’s life. In fact, from a hematologic standpoint, it behaves like MGUS, with a malignant transformation rate of 1% per year, with the exception of Alg

Figure 2. Light microscopy findings. (A) A representative glomerulus showing global nodular mesangial expansion by sclerosis and Ig deposits with mild mesangial hypercellularity. The nodules are periodic acid–Schiff (PAS) positive. There is segmental duplication of the glomerular basement membrane with cellular interposition (PAS stain). Magnification, ×400. (B) A different glomerulus showing similar nodular mesangial expansion. Some of the nodules stain black on silver stain, whereas others stain pink because of massive Ig deposits. Segmental duplication of the glomerular basement membrane is evident (arrow)(silver stain). Magnification, ×400.
amyloidosis (3,46). This needs to be kept in mind during treatment to maintain a risk-benefit ratio favorable to the patient. For example, persistent peripheral neuropathy may be acceptable to someone with MM but less so in someone with MGRS (76). Therefore, vigilant surveillance of adverse effects is essential. In addition, the goal of therapy, with the exception of AL amyloidosis, is preservation of kidney. Thus, a patient who has irreversible kidney damage

Figure 3. | Immunofluorescence findings. (A–C) There is (A) intense diffuse staining of glomerular mesangium, glomerular basement membranes, tubular basement membranes, and vessel walls for IgG, with negative staining for (B) \( \kappa \) and (C) \( \lambda \) in these locations. (D) There is bright glomerular basement membrane and mesangial staining for IgG1, with weaker focal tubular basement membrane and vessel wall staining for IgG1. Glomeruli were negative for IgG2 and IgG3 and showed only trace staining for IgG4 (not shown). Magnification, \( \times 200 \) in A and D; \( \times 100 \) in B and C.

Figure 4. | Electron microscopic findings. (A) Mesangial areas are expanded by abundant fine, granular, powdery, electron–dense deposits. Magnification, \( \times 15,000 \). (B) Similar deposits are seen segmentally involving the inner aspect of the glomerular basement membranes. Magnification, \( \times 10,000 \).
should not receive cytotoxic therapy, especially drugs with severe adverse effects, unless it is to achieve a complete response to minimize the risk of recurrence after kidney transplantation (49). In these cases, the patient should have been deemed an acceptable candidate for kidney transplantation.

The specific treatment of MGRS-related nephropathies is beyond the scope of this article and will not be discussed. It is important to understand the treatment of malignant hematologic diseases, which is changing quite rapidly. New therapies and paradigms are constantly being updated. The optimal treatment of these patients requires the hematologist to have a good understanding of the behavior and biology of the clones, the long-term consequences of the treatment, and the risks and benefits of the treatment. It also requires the nephrologist to monitor the natural history of the kidney disease and assess renal response to help guide therapy. This is particularly important in patients with PGNMID who may not have a detectable monoclonal protein for assessment of hematologic response. Pathologists from both disciplines are needed to help make the diagnosis of MGRS–associated kidney conditions and identify the pathologic clone. It is difficult for any one person to have all of the necessary expertise from bone marrow to the kidney to manage these patients by themselves. Aside from assessing response from both the hematologic and renal standpoints, the goal of therapy, the level of response, the acceptable adverse effects, and the long-term plan should be discussed and agreed on early. This cooperation not only helps define the parameters but sets clear goals for the clinicians and patient. This collaboration with my colleagues has been extremely helpful.

Questions

Insara Jaffer Sathick, MBBS (Nephrology Fellow at Mayo Clinic)

At which point in the diagnostic process for MGRS should the nephrologist initiate the full hematologic workup (bone marrow, flow cytometry, etc.) and/or consult the hematologist?

Answer

After an MGRS–associated nephropathy is diagnosed, a full hematologic evaluation should be performed to identify the clone responsible for the MGRS. The workup should begin with a bone marrow biopsy. In most patients, this is sufficient for clonal identification. Flow cytometry is important for identification of smaller clones that may be missed by histology. It is important to remember that the presence of clonal plasma cells, even when it is <5% of the marrow cellularity, is not normal. For lymphoma, the bone marrow may be negative, and a lymph node biopsy may be necessary. A positron emission tomography–computed tomography may be helpful in locating adenopathy. A hematologist/oncologist should be consulted for treatment of the clonal disease.

Kamel A. Gharaibeh, MD (Nephrology Fellow at Mayo Clinic)

For C3GN, how far do you go to rule out monoclonal protein as an underlying cause (assuming that the paraffin immunofluorescence after protease digestion is negative for Ig), and would you perform a bone marrow biopsy if the serum/urine testing is negative?

Answer

In a study of 32 patients with C3GN, ten were found to have an MG. Of these, two were found to have a C3nef, where six had three high-risk alleles identified. No autoantibodies were identified. In a separate series of six patients, one patient had an autoantibody to complement factor H, and two patients had complement factor H 402 allele, which is associated with dense deposit disease. No patients in this series had a C3nef. These two studies suggest that, although MG and C3GN can coexist, the monoclonal protein may not be responsible for the C3 deposition. Recently, the use of immunofluorescence on protease–digested, paraffin–embedded, formalin–fixed tissue was able to identify masked Ig in patients with C3GN and membranoproliferative GN (32). This should be performed on all patients with C3GN, especially if a monoclonal protein is present. Complement testing should also be performed to look for autoantibodies, C3nef, and gene alterations. Full hematologic workup should be performed on patients with autoantibodies or C3nef that matches the monoclonal Ig.

Abdurrhaman M. Hamadah, MD (Nephrology Fellow at Mayo Clinic)

How should patients who have a monoclonal protein–related kidney disease but no evidence of clone on bone marrow biopsy be managed?

Answer

Our previous study has shown that these patients do not have detectable monoclonal proteins either. This poses a particular challenge, because these patients do not possess hematologic biomarkers for assessment of response. The response to treatment can only be assessed by improvement in renal parameters, such as proteinuria and/or renal function. Renal response should be assessed no less often than every 2 months to guide therapy. Treatment should be discontinued if there is very good renal response, onset of adverse events, or lack of response to therapy.

Disclosures

None.

References


Abnormal Kidney Function and Urinary Light Chain, Leung et al. 9


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