Monoclonal gammopathy of renal significance

Hany Shaker Ali Mohamad; Sabry Abd-Allah Mohamad Shoaib; Mohamad Ahmad Mohamad Abd El-Hafez

Internal Medicine Department, Faculty of Medicine, Menoufia University, Egypt
dr_hany2004@yahoo.com

Abstract: Background: monoclonal gammopathy is an immune disease with immune-globulin or part of it is produced by clonal propagation of cells in B-lymphocytes. Its role in renal disease is recently studied. However, the field had many gaps in the understanding of the disease. **Aim of the work:** to study the role of monoclonal gammopathy of renal importance. **Methods:** an internet based search during the last 20 years with a keyword search of monoclonal gammopathy in the title of papers was done. Studies with sufficient data about the topic were thoroughly reviewed and the important results were included in the present work. **Results:** monoclonal immunoglobulins were found to have the ability to lead to different renal disorders resulting from the direct renal deposition of the monoclonal imuunoglobulin (MIg), and rarely from an indirect mechanism via dysregulation of the alternative pathway of complement. **Conclusion:** The monoclonal gammopathy-associated renal diseases are distinct in their pathogenesis, kidney biopsy findings, clinical presentation, progression, prognosis, and treatment. A thorough and complete evaluation of the MIg-associated renal disease needs to be performed to appropriately.
[Hany Shaker Ali Mohamad; Sabry Abd-Allah Mohamad Shoaib; Mohamad Ahmad Mohamad Abd El-Hafez **Monoclonal gammopathy of renal significance.** *Stem Cell* 2017;8(2):85-94]. ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). http://www.sciencepub.net/stem. 14. doi:10.7537/marsscj080217.14.

Keywords: monoclonal; gammopathy; renal insufficiency; renal transplantation; immunoglobulins

Introduction

Monoclonal gammopathy is a disorder in which a monoclonal immune-globulin or its piece is manufactured by clonal propagation of cells in the B-lymphocyte lineage. The range of hematologic diseases able of creating a monoclonal gammopathy comprises monoclonal gammopathy of uncertain significance (MGUS), multiple myeloma (MM), plasmacytoma, Waldenstrm macro-globulinemia (WM), chronic lymphocytic lymphoma (CLL), and other low grade lymphomas. Of these, MGUS is the greatest public affecting 3% of patients age 50 years or older. It is defined by 3 criteria: <3 g/dL of monoclonal (M) protein, <10% plasma cells in the bone marrow, and no proof of the damage of different organs. While it is a recognized predecessor of malignant diseases of the blood, such MM, immunoglobulin light chain (AL) amyloidosis, and WM, affected populations usually affected by these diseases at an average rate of ~1% per **year (Kyle et al., 2006).**

As a consequence, most diseases populations never suffered from a malignant disease of plasma cell and thus, MGUS has extended a relatively benign reputation. Unluckily, this is not completely precise **(Glavey and Leung, 2016).**

In addition to the danger of malignant conversion, MG has been an extensive diversity of diseases that are not connected to direct invasive or damaging properties of the clone. In fact, in diseased persons with AL amyloidosis, one of the most fatal diseases, merely 8% of diseased populations achieve the standards (criteria) for MM showing that small clones are not only able of generating disorder but can also be quite risky **(Merlini and Stone, 2006).**

MG is most often noticed as an accidental discovery in patient's serum. The diagnosis of MG has amplified in modern ages, certainly linked to the better-quality screening modalities of populations with public diseases such as anemia, impairment of renal function, and the high sensitivity of modern assays. As a consequence, there is a steady increase in diagnosis of the clinical importance in its private right and its link with a number of clinical diseases, in which the monoclonal protein and not the clonal quantity is occupied as a causal issue. Some causal links surely occur; however, given the somewhat high prevalence of MGUS in the whole population, many reported disease links are perhaps co-existed **(Bida et al., 2009).**

So, vigilant deliberation of this fact in each patient clinical situation is needed. In addition, since by description MGUS cannot own end organ destruction, it should not be handled in the setting where a pathologic disorder is ascribed to the monoclonal gammopathy **(Glavey and Leung, 2016).**

Aim of the work

The target of this essay is to study the role of monoclonal gammopathy of renal importance.

Methods

An internet based search of databases including PubMed; science direct of Elsevier, springer link, Wiley online library was done with a keyword of monoclonal gammopathy in the title of the article. The search span included the last 20 years. In addition, the local libraries were included in the search (the search done by the researcher himself in subsequent visits). All founded articles were thoroughly reviewed. The significant data were included in the present work. The next sections represented a brief description of the results. The data were presented in two main chapters the first deals with general data of the topic and the second deals with the specific effects of monoclonal gammopathy in renal disease.

Normal structure of immunoglobulins

Immunoglobulins are antibodies composed of glycoproteins arranged as Z1 units. Each of these components comprises 4 polypeptide chains: 2 equal heavy chains and 2 identical light chains **(Al-Hussain et al., 2015).**

Production of immunoglobulins

Immunoglobulins are usually manufactured in a reaction to exposure to foreign materials (antigens), such as microbes, viruses, fungi, and a diversity of other protein particles. Each B cell is able to produce a solitary class of antibody, categorized by a sole antigen binding site. A naive or memory B cell is stimulated by contact with an antigen corresponding to its superficial receptor, following which the cell multiplies (with the assistance of a helper T cell), and differentiates into an antibody-secreting effector cell **(Al-Hussain et al., 2015).**

Clinical spectrum of monoclonal gammopathy

1. Nephropathies:

Renal damage is a diagnostic factor of MM which is connected to an increased and early death and decreased the overall survival if present at diagnosis in MM **(Glavey et al., 2013).**

Cast nephropathy, acute tubular necrosis resulting from increased calcium levels (hypercalcemia) or use of nonsteroidal anti-inflammatory medications, AL amyloidosis, mono- clonal immune-globulin deposition disorder of the Randall type (MIDD), and light chain proximal tubulopathy (associated with or not associated with Fanconi syndrome) have all been found with multiple myeloma (MM) as causes of decreased renal function. However, more and more pathological renal diseases are ascertained to clonal plasma cell diseases that do not meet the diagnostic standards for MM. Unfortunately, glomerulo-nephritis that occurred in the lack of MM were misclassified and undertreated **(Gertz et al., 2009).**

2. Dermopathies:

Skin findings of MG have been well described. Remarkably, bulk really includes small clones. Cryoglobulins are categorized into 3 kinds on the basis of the structure of the immunoglobulins. Type I involve only monoclonal immunoglobulins. Type II and III are mixed where a monoclonal IgM (II) or polyclonal immunoglobulins (III) bind polyclonal IgG in a rheumatoid factor style. Of the three categories of cryoglobulins, type I and II are linked to monoclonal immunoglobulins; however, cutaneous manifestations which is connected to vacuities are more common in type II and III whereas type I is more linked with hyperviscosity. The typical sing at diagnosis is petechiae in the lower extremities. These can outspread to the trunk and both arms. They may also merge into purpura **(Ramos-Casals et al., 2012).**

Other disorders seem to be linked to a precise monoclonal antibody. Urticarial eruptions of the skin are found as a constituent of Schnitzler syndrome, which is a rare long-lasting, recurring urticarial rash associated with the existence of a monoclonal IgM gammopathy **(Barbosa et al., 2015).**

3. Neuropathy:

Neuropathy (either peripheral or central) is a well-defined problem associated with monoclonal gammopathy. Studies suggested that, up to 10% of population with peripheral neuropathy have symptomatic neuropathy at the phase of diagnosis. In MM, the prevalence can be increased to 20% at presentation and upsurges to 75% after therapy due to neurotoxic chemotherapies **(Raheja et al., 2015).**

4. Autoimmune disorders:

Given the irregular manufacture of immunoglobulin in MGUS it is probable that this immunoglobulin can react with self-antigen and appear clinically in diverse pictures. The monoclonal immunoglobulin formed by the B-cell clone can induce an autoimmune antibody that reacts with self-antigen. This has been reported to share in the progress of an insulin-linked autoimmune disorder, which occurs when the monoclonal immunoglobulin binds to human insulin. This results in an early postprandial increase of serum glucose (hyperglycemia), followed by a reactive overshoot in insulin production, as a consequence of hypertrophied or hyperplastic islet beta cells and later decreasing glucose values, or an unpredictable detachment of insulin from the complex, and a resultant upsurge in free levels of insulin with severe hypoglycemia several hours later. Manifestations can be serious ranging from sweating, dizziness, headache, and tremors to

confusion, seizures, and unconsciousness. The monoclonal anti-insulin immunoglobulin in monoclonal gammopathy has a lower affinity for insulin, but has a great capability for insulin-binding, leading to the disease of episodic hypoglycemic outbreaks. The insulin binding action of the monoclonal antibody has been evidently found in a number of described case reports **(Lichtman and Balderman, 2015).**

5. Ocular manifestations:

In a minority of diseased populations, the core monoclonal gammopathy can be accompanied by ocular diseases. Alertness of this connection is vital to confirm that populations are screened for the existence of a monoclonal protein. In patients with severe ocular disease, therapy of the eye disease and the monoclonal gammopathy may be necessary. Also, doctors following people with MGUS should be alert for the likelihood of progression of eye injury, so as to intervene, if possible, before damage is advanced. This is principally imperative in the eye injury given the complications threaten the sight. Monoclonal gammopathy associated with ocular disorder has been reported in different diseases including crystalline keratopathy, crystal-storing histiocytosis, hypercupremic keratopathy, and maculopathy. Given that ocular disease is due to the physicochemical properties of the MG, it can occur with or without overt MM or lymphoma **(de Alba et al., 2009).** Crystalline keratopathy may be existed in up to 1% of people with MG and MM. Crystals form as a product of immunoglobulin light chain precipitation within cells in the epithelial and stromal coats of the cornea **(Koo et al., 2011).**

6. Immunodeficiency:

Infection is a main factor to illness and is the important reason of death in multiple myeloma **(Nucci and Anaissie, 2009).** This is often ascertained to therapy of the disease but also to disease related immune- deficiency. MM-related immunodeficiency includes B-cell malfunction, such as hypo-gammaglobulinemia, as well as T-cell, dendritic cell, and NK-cell abnormalities. Given that plasma cell malfunction may be exist at the MGUS grade, it is possible that this complaint may also affect immune function. Different studies have shown an increased hazard risk of infections in people with MGUS, emphasizing the involvement of the underlying plasma cell disease to the immunodeficiency **(Pratt et al., 2007).**

7. Coagulopathy:

A. Thromboembolism:

Thromboembolism of venous system is a public comorbidity occurring in people with cancer and is the second leading cause of mortality in cancer patients treated by chemotherapeutic agents. Although, more commonly linked to solid cancers, a high frequency of VTE also occurs in hematological malignancies **(Khorana et al., 2007).** MM has a VTE frequency of about 10%, caused by a number of factors, comprising increased viscosity of the plasma, higher values of immunoglobulins in the circulation and the procoagulant action of the monoclonal protein. The frequency of VTE is also high in MGUS people with a hazard ratio of 3.4 at one year following diagnosis in a cohort of 5326 MGUS patients. Interestingly, the threat of arterial thrombosis is amplified in this category of patients with a 1-year hazard ratio of about 1.7 **(Zamagni et al., 2011).**

B. Acquired von Willebrand disease:

In a very small percentage of patients, the monoclonal immunoglobulin has characteristics of an autoantibody that may deactivate serious proteins. This has been found to be the situation in acquired von Willebrand disorder (AVWS) secondary to monoclonal protein and this is a well-known and characterized clinical entity. AVWS is a rare bleeding disorder associated with hemato-proliferative disorders, autoimmune conditions, neoplasia and cardiovascular disorders that often provide a challenge at diagnosis **(Tiede et al., 2011).**

8. Multi-systemic disease

A. AL amyloidosis:

The most known multi-systemic disorder found in association with monoclonal gammopathy is AL amyloidosis. It is the first disease where cytotoxic mediators are regularly used regardless of the fact that the bulk of people do not meet standard criteria for MM. While 40% of diseased subjects have 10% bone marrow plasma cells, only 8% meet standard criteria of symptomatic MM. AL amyloidosis can also be the end result of CLL and low grade lymphomas particularly lymphoplasmacytic lymphoma-manufacturing WM **(Strati et al., 2015; Chauvet et al., 2015).**

B. POEMS syndrome:

POEMS syndrome is other sample of the widespread toxicity monoclonal protein can possess. As the name proposes, it often includes the peripheral nerves, endocrine, and cutaneous structures. However, these people also had papilledema, extravascular volume overload, sclerotic bone injuries and thrombocytosis/ erythrocytosis (PEST). Lesions of the kidney have also been defined but monoclonal immunoglobulin precipitates are not identified **(Higashi et al., 2012).** The damage in POEMS may be

the effect of vascular endothelial growth factor (VEGF) and Interleukin (IL)-6 activation, both of which are now part of the diagnostic criteria. Both VEGF and IL-6 are used to observe response to treatment. The source of the monoclonal protein (lambda restricted in N90% of cases) is often from clonal cells of plasma in the bone marrow which averages 4% **(Dispenzieri, 2015).**

C. CANOMAD:

CANOMAD is a disorder including chronic ataxic neuropathy, ophthalmoplegia, M protein and agglutination and disialosyl antibodies **(Delmont et al., 2010).** These people complaining of sensorimotor neuropathy of upper and lower limbs, dysarthria, dysphagia, diplopia, bulbar and ataxic gait. The monoclonal immunoglobulin is usually an IgM but IgG has been found. The monoclonal protein can react to any one of the gangliosides like GM1, GD1a, GD2, GD1b, GT1b, GQ1b, GR1b and GD3. A cold agglutinin is also often found. Anti- myelin-associated-glycoprotein (anti-MAG) antibodies have also been described in the main bulk of patients. Findings on electromyogram are non-diagnostic and may or may not reveal a demyelination. Dorsal root ganglionopathy was described on autopsy of one diseased person **(McKelvie et al., 2013).**

Aside from the neurologic manifestations, an immune complex- mediated glomerulonephritis has been found which can exist with nephrotic syndrome. Treatment with IVIG is effective in most patients. Rituximab can be used in association with IVIG in refractory conditions **(Loscher et al., 2013).**

D. TEMPI syndrome:

TEMPI disorder is a relatively recent addition to the monoclonal gammopathy associated condition family **(Sykes et al., 2011).** These people complaining from telangiectasia, increased erythropoietin values with subsequent erythrocytosis, monoclonal gammopathy, perinephric fluid collections and intrapulmonary shunting. The telangiectasia can include the face, trunk and arms. Other manifestations consisted of dyspnea, flank fullness or pain. Erythropoietin levels exceeding 5000mU/mL have been recorded. Most cases reported so far involved a monoclonal IgG. In addition to clonal plasma cells, erythroid hyperplasia can be shown in the bone marrow without evidence of polycythemia vera or myeloproliferative neoplasm such as megakaryocytic hyperchromia or clustering, increased reticulin fibrosis, osteosclerosis, or intrasinusoidal hematopoiesis. Molecular examination for the JAK2 V617F mutation have been reliable negative **(Rosado et al., 2015).**

Monoclonal Gammopathy of Renal Significance

Kidney disorders, once linked to multiple myeloma or lymphoma, are now defined to be able of developing independently of the malignancy. Only about 15 % of AL amyloidosis and 20-65 % of MIDD people accomplish the standard criteria for multiple myeloma or lymphoma **(Nasr et al., 2012).**

Many of these populations never advance to multiple myeloma. In fact, their biology is more analogous to monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma than multiple myeloma. However, the use of the word MGUS in these populations is problematic and may lead to confusion. First, the word MGUS represents undetermined importance and needs the lack of end-organ destruction. In these populations, the importance of kidney damage has been established. Furthermore, the available guidelines regarding the therapy of plasma cell diseases clearly recommend against treating populations with MGUS **(Kyle et al., 2010).**

This makes sense in true MGUS populations where there is no end-organ destruction and the conversion frequency to multiple myeloma or other more serious complications is low. This is not relevant to populations who have pathologic lesions attributable to their monoclonal gammopathy. The contradiction arises from the term MGUS make it unsuitable for these diseased persons. As a result, a new term monoclonal gammopathy of renal significance (MGRS) has been founded to improve the classification of these patients and avoid confusion **(Leung and Nasr, 2017).**

The main difference between MGRS and MGUS is the presence of a renal disease that is attributable to the monoclonal protein **(Leung et al., 2012).** Both conditions are characterized by less than 10 % clonal plasma cells in the bone marrow, <3 g/dl of monoclonal (M) protein and the absenteeism of other defining features of multiple myeloma such as increased calcium levels (hypercalcemia), anemia, and bone lesions. However, where there is no end-organ destruction in MGUS, there is no renal injury by the monoclonal protein in MGRS. This is most often as a result of deposition of monoclonal immunoglobins, but monoclonal protein can also affect the kidney by other means such as activation of the complement system. Regardless of the pathophysiology, this direct link between the kidney and the monoclonal protein is what defines MGRS. By definition, cast nephropathy is not a MGRS-related renal disease as it is almost always associated with multiple myeloma **(Drayson et al., 2006).**

1- MGRS-related renal disorders with organized monoclonal immunoglobulin precipitates

A- AL Amyloidosis:

In systemic AL amyloidosis, kidney is the common involved organ. An abnormal creatinine value is seen in about half of diseased populations. Proteinuria and nephrotic syndrome are found in 73 and 28 %, respectively. Median proteinuria is 5.8 g/d. The proteinuria is mainly consisted of albuminuria, which makes up on average 70 % of the urinary proteins **(Leung et al., 2012).** In a small percentage of patients, a vascular-limited AL amyloidosis has been found, which presents with progressive renal failure but little (<1 g/d) or no proteinuria **(Eirin et al., 2012).**

B- Immunotactoid Glomerulonephritis:

Immunotactoid glomerulonephritis (ITG) is a rare renal disorder characterized by the precipitation of microtubules in the glomerulus. Unlike amyloid, these fibrils are much larger and do not stain with Congo red. The average diameter of immunotactoid fibrils is 38.2 nm with a frequency of 20-55 nm. The most unique feature, however, is the hollow center, which is like to microtubules. Other fibrils with like manifestations are cryoglobulins, thus by definition, cryoglobulinemia must be ruled out. Historically, fibrillary glomerulonephritis has been defined together with ITG and was once thought to the same disorder. Histologically, they do share common manifestations such as membranoproliferative pattern with endocapillary propagation, mesangial expansion and hypercellularity, membranous-like pattern, even hyaline pseudothrombi in the glomeruli and crescents **(Nasr et al., 2012).** Major differences include smaller fibril size in fibrillary glomerulonephritis. The fibrils are hard and randomly arranged in fibrillary glomerulonephritis whereas the microtubules in ITG are hollow and usually arranged in parallel arrays **(Bridoux et al., 2002).** More prominently, ITG microtubules are usually composed of complete monoclonal immunoglobulins while fibrillary glomerulonephritis is rarely monoclonal **(Nasr et al., 2011).**

C- Light-Chain Fanconi Syndrome:

Light-chain Fanconi syndrome (LCFS) is a rare disease manifestated by electrolyte irregularities as a result of proximal tubular injury. The injury is due to intracellular crystalline precipitation of monoclonal light chains. Fanconi syndrome and proximal tubular cytoplasmic deposits may also be existing in crystal-storing histiocytosis (CSH). The latter, however, is different from LCFS in that the deposits are mainly found within the cytoplasm of histiocytes in the kidney interstitium, bone marrow, and other organs. Like CSH, nearly 90 % of the patients of LCFS are kappa restricted with VkI being the commonest subtype **(Messiaen et al., 2000).** Multiple myeloma is found in about half of the diseased people with smaller percentage of diseased persons diagnosed with WM, CLL, smoldering MM, and MGRS. LCFS diseased persons often exist in their sixth decade with a median age of 57 years. It is to some extent more common in humans with 58 % male. Typical complaints include tubular proteinuria (usually not high grade), glycosuria, and renal insufficiency. Extrarenal presentations include bone ache, osteomalacia, and easy fatigability. Insufficiency fractures are also common. Many people will also ave electrolyte irregularities such as hypouricemia (66 %), hypophosphatemia (50 %), and hypokalemia (44 %), but these tend to fade as the kidney function impairs % **(Ma CX et al., 2004).**

D- Cryoglobulinemia:

In the kidney, cryoglobulinemia presents as glomerulonephritis with or without endovasculitis. The most common histologic pattern is membrano-proliferative glomerulonephritis, but mesangio- proliferative and endocapillary proliferative glomerulonephritis are also repeatedly observed. Even membranous outline has been described. Florid monocytic deposits of glomeruli is typical of cryoglobulinemic glomerulonephritis. Cryoglobulins can be seen forming pseudothrombi in the lumen of glomerular capillaries and may also be seen in the intima and lumina of arterioles and interlobular arteries, occasionally causing endovasculitis. On IF, the precipitates should stain for the monoclonal immunoglobulin involved in the cryoglobulins. C3 can also be found. Most people present with proteinuria and moderate renal impairment **(Tedeschi et al., 2007).** Only 20 % of people have nephrotic syndrome at diagnosis. Another 20- 30 % may complain of a nephritic picture with macro- or microhematuria. A small proportion will present like a rapidly progressive glomerulonephritis (RPGN) with quick loss of renal function. One striking feature of cryoglobulinemia is severe hypertension. Hypertension linked to cryo-globulinemia is often hard control. In fact, studies have found only 15 % of people with cryoglobulinemia died of renal failure, but they are much more likely to die of cardiovascular complications or infection. Treatment of cryoglobulinemia depends on the type and etiology. Anti-viral treatment has been effective for type II cryoglobulinemia secondary to hepatitis C. This can be combined with rituximab in severe cases **(Saadoun et al., 2010).**

2-MGRS-Related kidney disorder with non-organized monoclonal immunoglobulin deposition

A- Monoclonal immunoglobulin deposition disorder:

MIDD represents a group of renal disorders characterized by deposits of monoclonal immunoglobulin and its components. They include light-chain deposition disease (LCDD), light- and heavy-chain deposition disease (LHCDD), and heavy-chain deposition disease (HCDD). LCDD is the commonest subtype of MIDD. MIDD is seen in 5 % of MM people in autopsy series at approximately half the frequency of AL amyloidosis. The kidney is almost entirely affected while systemic involvement in the lungs, heart, liver, and other soft tissue is less common and often asymptomatic. The commonest malignant disease associated with MIDD is multiple myeloma found in 59-65 % of cases while CLL is found in 3 %. In the past, the rest of populations was defined as idiopathic **(Nasr et al., 2012).** However, one study revealed 100 % of the populations with MIDD had an abnormal serum FLC ratio signifying that these people would be more precisely classified as MGRS **(Leung et al., 2012).** The most distinguishing histological lesion in MIDD is nodular mesangial sclerosis. By light microscope, nodules are positive for PAS and silver similar Kimmelstiel-Wilson nodules of diabetic nephropathy. Other manifestations comprise mesangial sclerosis without nodules, membranoproliferative shape, and crescents. The deposits in MIDD are negative for Congo red. The most characteristic manifestations are seen on IF where monoclonal light chains, heavy chains or complete immunoglobulin can be found in a linear pattern along the GBM and even more consistently along the tubular basement membranes (TBM). Staining of the immunoglobulin components can be found in the mesangium, but it is less consistent than the TBM or GBM. C3 may also be founded in cases of LCHDD and HCDD. The deposits should not have any organized component on EM and should appear as powdery or amorphous electron-dense deposits in the same compartment as seen on IF. Occasionally, small fibers have been found **(Nasr et al., 2012).**

B- Membranoproliferative glomerulonephritis with monoclonal deposits:

Membrano-proliferative glomerulonephritis (MPGN) is a group of renal disorders that share a common histopathologic pattern of disease. MPGN conventionally had been classified by the location of the deposits. Of the three types, type II MPGN, also identified as dense deposit disease (DDD), had a unique pathophysiology. DDD is the result of abnormal complement activation resulting in the deposition of C3 **(Sethi et al., 2012).** MPGN secondary to infection, autoimmune disorders, malignancy and other complement dysregulation can present as either type I or III. The contribution of monoclonal gammopathy in the pathophysiology of MPGN was not recognized until recently. In a single-center study that excluded patients with hepatitis (B & C) and DDD found 41 % of the MPGN cases had a circulating monoclonal protein. Monoclonal protein deposits were defined in the kidney in most of those patients. While majority of the patients were MGRS, 21 % met standard criteria for multiple myeloma and another 17.8 % had WM, CLL, and other lymphomas **(Sethi et al., 2010).**

C-Proliferative glomerulonephritis with monoclonal IgG deposits:

A relatively new kidney disorder linked with MGRS is the proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) **(Nasr et al., 2009).** A sole manifestation of these people is their preference for monoclonal IgG3. IgG3- accounts for more than 50 % of cases, and IgG3- contributes to another ~13 % of patients. Hematologically, they tend to have a low clonal dirorder load. Less than 10 % of populations qualify for multiple myeloma and over half do not even have measurable circulating monoclonal protein. Despite that, they have a high rate of return after renal transplantation, which has been found as early as 3 months post-transplant **(Nasr et al., 2011).** These patients commonly complain of nephrotic syndrome (>50 %). Mean proteinuria is 5.7 g/d. Most will also have renal insufficiency with the median SCr of 2.8 mg/dl. Microscopic hematuria may be found in the majority of cases. Mean age at diagnosis was 54 years with 62 % females. During a mean follow-up of 30 months in one study, 21.9 % of the people developed ESRD and 15.6 % had been died. Response has been described with alkylator and steroids, rituximab, and steroids alone. Knowledge with anti-myeloma medications especially with newly introduced drugs is small, and effectiveness remains to be determined **(Nasr et al., 2009).**

3-MGRS-related kidney disease without monoclonal immune-globulin deposits

A- C3 Glomerulonephritis:

C3 glomerulonephritis (C3GN) is a subset of C3 glomerulopathy that comprises DDD and CFHR3 nephropathy **(Barbour et al., 2013).** It is manifested by deposits that are predominate C3 and without C1q, C4 or immunoglobulins. By light microscopy, it may show features of MPGN, mesangial proliferative glomerulonephritis or endocapillary proliferative glomerulonephritis. It may also display prominent glomerular neutrophil depositions mimicking postinfectious glomerulo- nephritis. Infiltrates can be

both subendothelial, subepithelial, and/or mesangial on EM. The appearance is, however, less electron dense than those of immunoglobulin deposits **(Sethi et al., 2012).**

B-Thrombotic microangiopathy in POEMS syndrome

POEMS syndrome also known as Crow-Fukase syndrome is multisystemic disease most commonly due to a lambda-restricted monoclonal gammopathy. The name POEMS is taken from 5 of the more common presentations, which include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin manifestations, and sclerotic bone lesions **(Dispenzieri, 2012).**

Additional manifestations include extravascular volume overload, thrombocytosis, elevated values of vascular endothelial growth factor (VEGF), and interleukin (IL)-6. The monoclonal protein is almost always lambda. This disorder mimics MGUS as the median proportion of plasma cells in the bone marrow is 5 %. POEMS syndrome can also arise from smoldering multiple myeloma, plasmacytoma, lympho-plasmacytic lymphoma, and Castleman disease. Renal manifestations are not noticeable manifestations in POEMS. Often, people may have renal impairment due to issues with volume. One sole manifestation is asymmetric size of the kidneys, which is believed to be due to unilateral renomegaly while other sensations it is due to unilateral atrophy **(Clapp et al., 2011).**

C- Recurrent disorders after kidney transplantation:

One common manifestation shared by all MGRS-related renal disorders is the high incidence of recurrence after renal transplantation. All glomerular disorders can recur after renal transplantation. Diseases such as membranous nephropathy and focal segmental glomerulo- sclerosis have recurrence incidence between 7 and 50% **(Sprangers and Kuypers, 2013).** Recurrence of IgA nephropathy could be high up to 61 % but loss of renal allograft is infrequent. Recurrence of ANCA-associated vasculitis is less than 10 % likely the consequence of immunosuppression **(Gera et al., 2007).** On the other hand, MGRS-related renal disorders can recur at >80 %. Often, this is in association with allograft damage and death of the patient, making renal transplantation problematic. The best example of the high recurrence incidence in MGRS-related renal diseases is MIDD. In one trial, 5 of 7 populations with LCDD developed recurrent disorder in their renal allograft. Median time for recurrence is 33 months with a range of 3-45 **(Leung et al., 2004)**

Diagnosis of MGRS-Related renal disorders

The definition of MGRS needs that the monoclonal gammopathy has a direct role in the pathogenesis of the renal disease **(Leung et al., 2012).** This can only be demonstrated by a kidney biopsy. This is principally important in people over the age of 60 where the incidence of MGUS exceeds the incidence of renal disorders **(Kyle et al., 2006).**

Treatment of MGRS

The risk of medication-related myelodysplastic syndrome was often too high to use cytotoxic therapy for MGRS-related renal diseases. The one exception was AL amyloidosis. Since it is able of being quickly fatal, cytotoxic medications including high-dose chemotherapy was accepted even for people without multiple myeloma **(Palladini et al., 2007).** The same method, however, was not experienced with the other MGRS-related renal diseases. In an Italian study of patients with MIDD, cases with multiple myeloma were more likely to take vincristine - doxorubicin - dexamethasone (VAD) or vincristine- doxorubicin-methyl- prednisolone (VAMP) than cases without multiple myeloma ($p = 0.007$) **(Pozzi et al., 2003).** Whether this practice affected the life of patients with MIDD without multiple myeloma was unclear, but the reduced renal recovery degree and high recurrence incidence after renal transplant were attributable to inadequate treatment **(Leung et al., 2004).** In disorders with low incidence of multiple myeloma such as PGNMID, myeloma therapy was rarely used **(Nasr et al., 2011).** Fortunately, the institution of new drugs in the management of multiple myeloma had improved the standpoints. First, concern of myelodysplastic syndrome is much less with new drugs than with alkylators. More significantly, the high and deep responses produced by novel drugs have changed the renal outcome in those populations **(Rajkumar, 2011).** The principles of treatment are: as much as possible, treatment should be tailored to each specific clone rather than the kidney disease. In people without a recognizable clone, the practical method is to start with cyclophosphamide, bortezomib, and steroids **(Fermand et al., 2013).** The use of bortezomib as a frontline drug is favored over other new drugs due to its rapid action, absence of nephrotoxicity or necessity for dosage adjustment in renal impairment **(Chanan-Khan et al., 2007).**

Since many of the MGRS-related disorders have low potential for malignant transformation, the primary aim of therapy for most patients (except AL amyloidosis) is conservation of renal function rather than life **(Leung et al., 2012).** Thus, for persons with advanced degree of renal damage with little prospect of renal recovery and no other systemic involvement, and who are not candidates for kidney transplantation,

treatment may not be necessary **(Fermand et al., 2013).** Alternatively, people with rapidly decreasing renal function should be managed in aggressive manner to prevent development of ESRD. Similarly, people with advanced chronic renal disease or ESRD who are appropriate for renal transplantation should be managed in order to reduce their likelihoods of recurrence after renal transplantation. One important aspect to bear in mind when managing these populations is the differentiation between hematologic response and renal response. While renal response is relied on hematologic response, it is also relied on the severity of the renal damage **(Leung et al., 2007).**

Kidneys with advanced disease may not recover in spite of attainment of complete hematologic response. Kidney transplantation has been hard due to the high incidence of recurrence and graft damage and unsuccessful and risky medications **(Leung et al., 2004).** Addition of alkylator medications to immune-suppression often resulted in over immune-suppression leading to infection and sepsis. The use of high-dose medications followed by autologous stem cell transplantation (SCT) has made it possible to perform renal transplantation in these patients. The attainment of hematologic complete response (CR) either prior to or after renal transplant has yielded acceptable outcomes in both allograft and patient survival in populations with AL amyloidosis **(Herrmann et al., 2011).** Similar policy has been successfully engaged in people with MIDD to prevent recurrence in the renal allograft **(Girnius et al., 2011).** In diseases with rapid recurrence, reaching of CR should be done before renal transplantation to avoid avoidable destruction to the kidney allograft. With the deep responses, new drugs are able of production, the question whether SCT is essential is valid and pertinent **(Mikhael et al., 2012).**

Conclusion

MIg can lead to different renal disorders resulting from the direct renal deposition of the MIg, and rarely from an indirect mechanism via dysregulation of the alternative pathway of complement. The monoclonal gammopathy-associated renal diseases are distinct in their pathogenesis, kidney biopsy findings, clinical presentation, progression, prognosis, and treatment. A thorough and complete evaluation of the MIg-associated renal disease needs to be performed to appropriately manage these patients.

References

1. Al-Hussain T, Hussein MH, Al Akhtar M. Renal Involvement in Monoclonal Gammopathy. Adv Anat Pathol 2015; 22:121–134.
2. Barbosa NS, Schoch JJ, Ringler MD, et al. Chronic urticarial eruption associated with monoclonal gammopathy. Am J Hematol 2015;90:365–6.
3. Barbour TD, Pickering MC, Cook HT. Recent insights into C3 glomerulopathy. Nephrol Dial Transplant Official Publ Eur Dial Transplant Assoc Eur Ren Assoc. 2013; 28(7):1685–93.
4. Bida JP, Kyle RA, Therneau TM, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. Mayo Clin Proc 2009; 84:685–93.
5. Bridoux F, Leung N, Hutchison CA, et al. Fibrillary glomerulonephritis and immunotactoid (microtubular) glomerulopathy are associated with distinct immunologic features. Kidney Int. 2002; 62(5):1764–75.
6. Chanan-Khan AA, et al. Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study. Blood 2007;109(6):2604–6.
7. Chauvet S, Bridoux F, Ecotiere L, et al. Kidney diseases associated with monoclonal immunoglobulin M-secreting B-cell lymphoproliferative disorders: a case series of 35 patients. Am J Kidney Dis 2015;66:756–67.
8. Clapp AJ, et al. Imaging evidence for renomegaly in patients with POEMS syndrome. Acad Radiol. 2011;18(10):1241–4.
9. de Alba Campomanes AG, Rutar T, Crawford JB, et al. Crystal-storing histiocytosis and crystalline keratopathy caused by monoclonal gammopathy of undetermined significance. Cornea 2009;28:1081–4.
10. Delmont E, Jeandel PY, Hubert AM, et al. Successful treatment with rituximab of one patient with CANOMAD neuropathy. J Neurol 2010; 257:655–7.
11. Dispenzieri A. How I treat POEMS syndrome. Blood 2012;119:5650–8.
12. Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. Am J Hematol 2015; 90:951–62.
13. Drayson M, et al. Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. Blood 2006;108(6):2013–9.
14. Eirin A, et al. Clinical features of patients with immunoglobulin light chain amyloidosis (AL) with vascular-limited deposition in the kidney. Nephrol Dial Transplant Official Publ Eur Dial Transplant Assoc Eur Ren Assoc. 2012;27(3):1097–101.
15. Fermand JP, Bridoux F, Kyle RA, et al. How I

treat monoclonal gammopathy of renal significance (MGRS). Blood 2013; 122:3583–90.
16. Gera M, et al. Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosupression. Kidney Int. 2007; 71(12):1296–301.
17. Gertz MA, Leung N, Lacy MQ, et al. Clinical outcome of immunoglobulin light chain amyloidosis affecting the kidney. Nephrol Dial Transplant 2009; 24:3132–7.
18. Girnius S, et al. Long-term outcome of patients with monoclonal Ig deposition disease treated with high-dose melphalan and stem cell transplantation. Bone Marrow Transplant. 2011;46(1):161–2.
19. Glavey SV, Gertz MA, Dispenzieri A, et al. Long-term outcome of patients with multiple [corrected] myeloma-related advanced renal failure following auto-SCT. Bone Marrow Transplant 2013; 48:1543–7.
20. Glavey SV, Leung N. Monoclonal gammopathy: The good, the bad and the ugly. Blood Reviews 2016; 30: 223–231.
21. Herrmann SM, Gertz MA, Stegall MD, et al. Long-term outcomes of patients with light chain amyloidosis (AL) after renal transplantation with or without stem cell transplantation. Nephrol Dial Transplant. 2011; 26(6): 2032-2036.
22. Higashi AY, et al. Serial renal biopsy findings in a case of POEMS syndrome with recurrent acute renal failure. Clin Experimental Nephrol. 2012;16(1):173–9.
23. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5:632–4.
24. Koo H, Oh DH, Chun YS, et al. A case of crystalline keratopathy in monoclonal gammopathy of undetermined significance (MGUS). Korean J Ophthalmol 2011; 25:202–5.
25. Kyle RA, Therneau TM, Rajkumar SV, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia. 2010; 24(6):1121–7.
26. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 2006; 354:1362–9.
27. Leung N, et al. Long-term outcome of renal transplantation in light-chain deposition disease. Am J Kidney Dis Official J National Kidney Found. 2004;43(1):147–53.
28. Leung N, et al. Severity of baseline proteinuria predicts renal response in immunoglobulin light chain-associated amyloidosis after autologous stem cell transplantation. Clin J Am Soc Nephrol CJASN. 2007;2(3):440–4.
29. Leung N, Nasr SH. Renal Disease Associated with Monoclonal Gammopathy. Chapter 9, IN: T.M. Zimmerman and S.K. Kumar (eds.), Biology and Management of Unusual Plasma Cell Dyscrasias, Springer Science+Business Media New York 2017; pp 163-194.
30. Leung N, Bridoux F, Hutchison CA, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood 2012;120:4292–5.
31. Lichtman MA, Balderman SR. Unusual manifestations of essential monoclonal gammopathy. II. Simulation of the insulin autoimmune syndrome. Rambam Maimonides Med J 2015:6. http://dx.doi.org/ 10.5041/ RMMJ.10212.
32. Loscher WN, Woertz A, Wallnofer M, et al. Successful treatment of CANOMAD with IVIg and rituximab. J Neurol 2013;260:1168–70.
33. Ma CX, et al. Acquired Fanconi syndrome is an indolent disorder in the absence of overt multiple myeloma. Blood. 2004;104(1):40–2.
34. McKelvie PA, Gates PC, Day T. CANOMAD: report of a case with a 40-year history and autopsy. Is this a sensory ganglionopathy with neuromuscular junction blockade? Muscle Nerve 2013; 48:599–603.
35. Merlini G, Stone MJ. Dangerous small B-cell clones. Blood 2006;108:2520–30.
36. Messiaen T, Deret S, Mougenot B, et al. Adult Fanconi syndrome secondary to light chain gammopathy. Clinicopathologic heterogeneity and unusual features in 11 patients. Medicine (Baltimore). 2000;79(3):135-154.
37. Mikhael JR, Schuster SR, Jimenez-Zepeda VH. Cyclophosphamide-bortezomibdexamethasone (Cy Bor D) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood 2012; 119:4391–4.
38. Nasr SH, Satoskar A, Markowitz GS. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol 2009;20:2055–64.
39. Nasr SH, Sethi S, Cornell LD, et al. Proliferative glomerulonephritis with monoclonal IgG deposits recurs in the allograft. Clin J Am Soc Nephrol 2011;6:122–32.
40. Nasr SH, Valeri AM, Cornell LD, et al. Renal monoclonal immunoglobulin deposition disease: a report of 64 patients from a single institution. Clin J Am Soc Nephrol 2012;7:231–9.
41. Nucci M, Anaissie E. Infections in patients with

multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis 2009;49:1211–25.
42. Pozzi C, et al. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. Am J Kidney Dis Official J National Kidney Found. 2003;42(6):1154–63.
43. Pratt G, Goodyear O, Moss P. Immunodeficiency and immune-therapy in multiple myeloma. Br J Haematol 2007; 138:563–79.
44. Raheja D, Specht C, Simmons Z. Paraproteinemic neuropathies. Muscle Nerve 2015; 51:1–13.
45. Rajkumar SV. Treatment of multiple myeloma. Nature reviews. Clinical oncology. 2011;8(8):479–91.
46. Ramos-Casals M, Stone JH, Cid MC, et al. The cryoglobulinaemias. Lancet 2012;379: 348–60.
47. Rosado FG, Oliveira JL, Sohani AR, et al. Bone marrow findings of the newly described TEMPI syndrome: when erythrocytosis and plasma cell dyscrasia coexist. Mod Pathol 2015; 28:367–72.
48. Saadoun D, et al. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. Blood. 2010;116(3):326–34; quiz 504–5.
49. Sethi S, et al. Dense deposit disease associated with monoclonal gammopathy of undetermined significance. Am J Kidney Dis. 2010;56 (5):977–82.
50. Sethi S, Nester CM, Smith RJ. Membranoproliferative glomerulo-nephritis and C3 glomerulopathy: resolving the confusion. Kidney Int. 2012; 81 (5):434–41.
51. Sprangers B, Kuypers DR. Recurrence of glomerulonephritis after renal transplantation. Transplant Rev. 2013;27(4):126–34.
52. Strati P, Nasr SH, Leung N, et al. Renal complications in chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis: the Mayo Clinic experience. Haematologica 2015;100:1180–8.
53. Sykes DB, Schroyens W, O'Connell C. The TEMPI syndrome—a novel multisystem disease. N Engl J Med 2011;365:475–7.
54. Tedeschi A, et al. Cryoglobulinemia. Blood Rev. 2007;21(4):183–200.
55. Tiede A, Rand JH, Budde U, et al. How I treat the acquired von Willebrand syndrome. Blood 2011;117:6777–85.
56. Zamagni E, Brioli A, Tacchetti P, et al. Multiple myeloma, venous thromboembolism, and treatment-related risk of thrombosis. Semin Thromb Hemost 2011;37: 209–19.

5/13/2017