

THE MONOCLONAL GAMMOPATHIES OF RENAL SIGNIFICANCE

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Abstract

As a heterogeneous group of diseases, monoclonal gammopathy is typical for older age and is characterized by the presence of paraprotein in serum and urine. In addition to damage to the bone marrow, other organs are also affected, whereas in the case of monoclonal gammopathy of renal significance (MGRS), the kidneys are dominant. The clinical presentation of MGRS is diverse depending on the type of renal monoclonal gammopathy. The basis of the diagnosis is the detection of free light chains in the serum, along with electrophoresis and subsequent serum immunofixation. The kappa and lambda serum light chain ratio is evaluated in patients with MGRS within modified reference parameters. A kidney biopsy provides information on the extent of renal parenchymal involvement. The basis of therapy is chemotherapeutics with possible autologous stem cell transplantation to preserve kidney function.

Keywords: monoclonal gammopathies, free light chains, kappa/lambda ratio

Abbreviations

AKI – acute kidney injury

AL – amyloidosis of light chains

ASCT – autologous stem cell transplantation

CKD – chronic kidney disease

CT – Computer Tomography

eGFR – estimate glomerular filtration rate

ELFO – electroforesis

ESKD – end-stage kidney disease

FLC – free light chains

IFX – immunofixation

Ig – immunoglobulin

IKMG – International Kidney & Monoclonal Gammopathy Research Group

IMWG – International Myeloma Working Group

LCDD – Light chain deposition disease

MG – monoclonal gammopathy

MGCS – monoclonal gammopathy of clinical significance

MGNS – monoclonal gammopathy of neurological significance

MGRS – monoclonal gammopathy of renal significance

MGUS – monoclonal gammopathy of undetermined significance

MM – multiple myeloma

MRI – magnetic resonance imaging

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PET – Positron Emission Tomography

POEMS – polyneuropathy, organomegaly, endocrinopathy, MG and skin changes

SPEP – serum protein electrophoresis

κ/λ – kappa a lambda ratio

INTRODUCTION

Monoclonal gammopathy (MG) represents a heterogeneous group of diseases characterized by the presence of monoclonal immunoglobulin (paraprotein, M-protein) in serum or urine, which is produced by clonal plasma cells, plasmacytoid lymphocytes, or differentiated B-lymphocytes. MG includes monoclonal gammopathy of undetermined significance (MGUS), monoclonal gammopathy of clinical significance (MGCS), multiple myeloma (MM), light chain amyloidosis (AL), non-Hodgkin's lymphoma, and many other diseases that go beyond the scope of this article (1, 2).

The prevalence of MG increases with age and reaches a value of 3.2% in the population of patients over 50 years of age. MG is generally considered a precancerous condition of MM. However, MG can cause secondary organ damage even before malignant transformation occurs. The essence of the mechanism is the deposition of monoclonal immunoglobulins or amyloid fibrils (AL amyloidosis), abnormal complement activation (e.g. C3-glomerulonephritis, atypical hemolytic-uremic syndrome), or autoantibody activity of immunoglobulins (e.g. IgM-associated neuropathy). The result is organ damage with an increased incidence of other organ diagnoses with a given clinical correlate. We refer to this phenomenon as MGCS, where we include AL amyloidosis, monoclonal gammopathy of renal significance (MGRS – monoclonal gammopathy of renal significance), monoclonal gammopathy of neurological significance (MGNS – monoclonal gammopathy of neurological significance), and monoclonal gammopathy of cutaneous significance. The review publication aims to present the clinical picture and the latest diagnostic and therapeutic trends of MGRS (3).

Definition and etiopathogenesis

The International Kidney & Monoclonal Gammopathy Research Group (IKMG) defines MGRS as the presence of ≥ 1 renal lesions caused by deposits of monoclonal immunoglobulins (or components). In contrast, monoclonal B-lymphocyte lines do not cause tumour complications, nor are haematological criteria for specific therapy met (4).

The most common cause of MG affecting the kidneys is MM. Under physiological conditions, B-lymphocytes produce 500 mg of polyclonal free light chains (FLC) immunoglobulins daily. In comparison, only 1–10 mg of FLC reaches the primary urine, thanks to the proximal tubule's highly efficient multiligand endocytic receptors (megalin, Dublin). However, with the dysregulated monoclonal formation of FLC, the capacity of the receptors is exceeded many times with a subsequent increase in the concentration in the ultrafiltrate and definitive urine (Bence-Jones protein). In this context, we discuss the toxic level of FLC, which varies from study to study. However, according to the IKMG, toxicity is set at ≥ 500 mg/l, confirmed by the study of Yadav et al. in 2020. The result is isolated damage to the proximal tubules, cast nephropathy (myeloma kidney), or a combination of both. FLCs have a direct toxic effect on the cells of the proximal tubules, where excessive endocytosis activates apoptotic and redox pathways, proinflammatory (interleukin 6, 8) transcription, and profibrotic cytokines (transforming growth factor $\beta 1$). The result is the initiation of an inflammatory cascade with subsequent tubulointerstitial fibrosis. The formation of casts usually occurs in the distal tubule after binding FLC to the domain of uromodulin (Tamm-Horsfall protein) with subsequent blockage of ultrafiltrate flow, resulting in tubular atrophy and interstitial fibrosis. Dehydration, diuretics, hypercalcemia, nephrotoxic drugs (aminoglycoside antibiotics, nonsteroid antibiotic drugs), and contrast agents contribute to FLC toxicity (5, 6, 7).

Clinical course

MGRS presents with a wide range of clinical symptoms. Depending on the type of MGRS, we meet patients with proteinuria - nephrotic and nephritic syndrome, hematuria, arterial hypertension, acute kidney injury (AKI), or the development of chronic kidney disease (CKD – chronic kidney disease).

In addition to those mentioned, toxic paraprotein also affects other organ systems with extrarenal manifestation. Cardiac, hepatic, and neurological damage may also occur in patients with AL amyloidosis. In some cases of MGRS, there is the release of endothelial growth factors or dysregulation of the alternative complement pathway, which may manifest as thrombotic microangiopathy, skin lesions, or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, MG, and skin changes). In the case of MM, the clinical picture is conditioned by the presence of paraprotein and the accumulation of myeloma cells. The most common and first symptom of MM is bone pain (67%), followed by general weakness (14%), chronic fatigue (9%), dyspnea (5%), and weight loss (5%). Due to the age group of patients for which the occurrence of MM is typical, back pain is attributed to older age, which often leads to a delay in diagnosis. Bone lesions are an essential diagnostic criterion for MM, as shown in Table 1 (8, 9, 10, 11, 12).

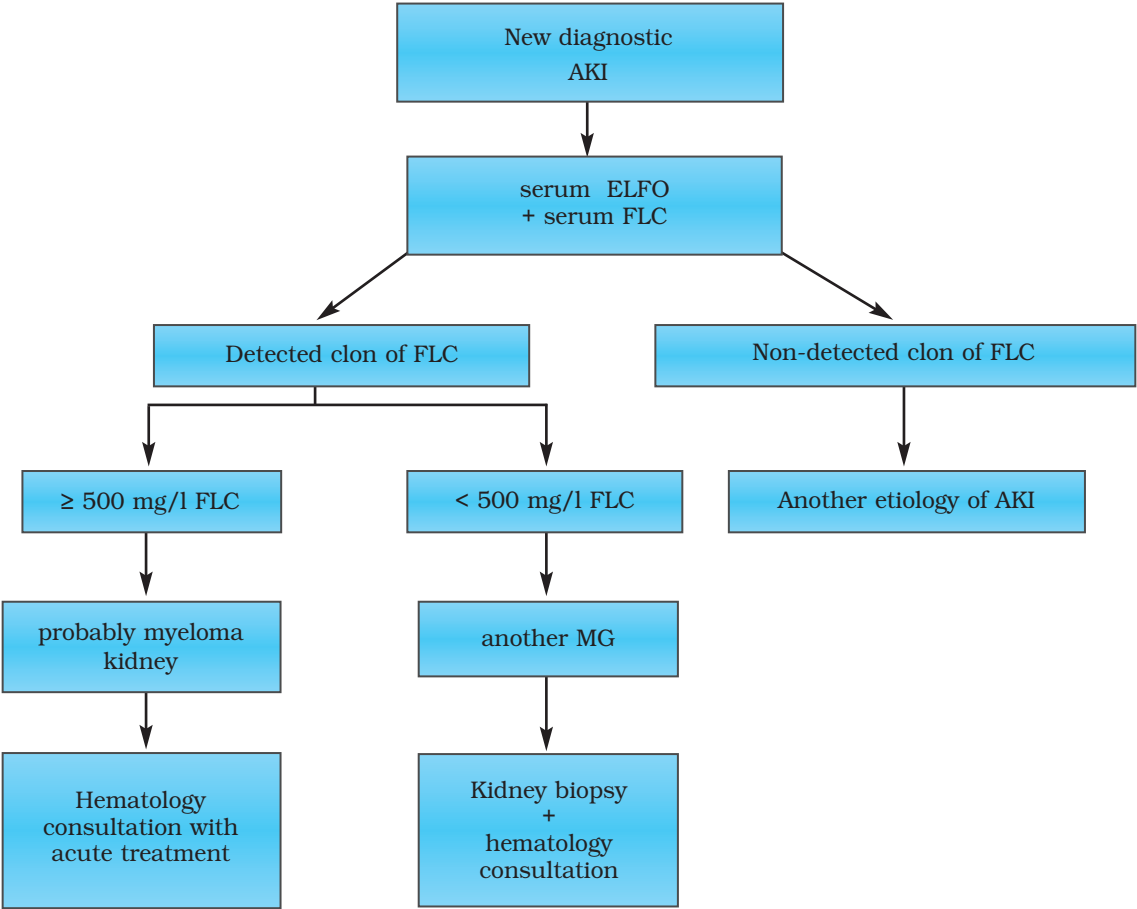
Table 1 Diagnostic criteria for multiple myeloma (11)

Criteria	Definition
Sixty %	60 % plasma cell infiltration in bone marrow
Light chain	FLC κ/λ ratio > 100
MRI	> 1 focal bone lesion
Calcium	Hypercalcemia > 2.75 mmol/l or > 0.25 mmol/l above upper limit of normal
Renal insufficiency	Creatinine > 173 $\mu\text{mol/l}$ or creatinine clearance < 40ml/min
Anemia	Hb < 100 g/l or > 20g/l below lower limit of normal
Bone lesions	≥ 1 osteolysis on skeletal radiography: X-ray, CT or PET/CT

FLC – free light chains, MRI – magnetic resonance imaging, CT –Computer Tomography, PET –Positron Emission Tomography

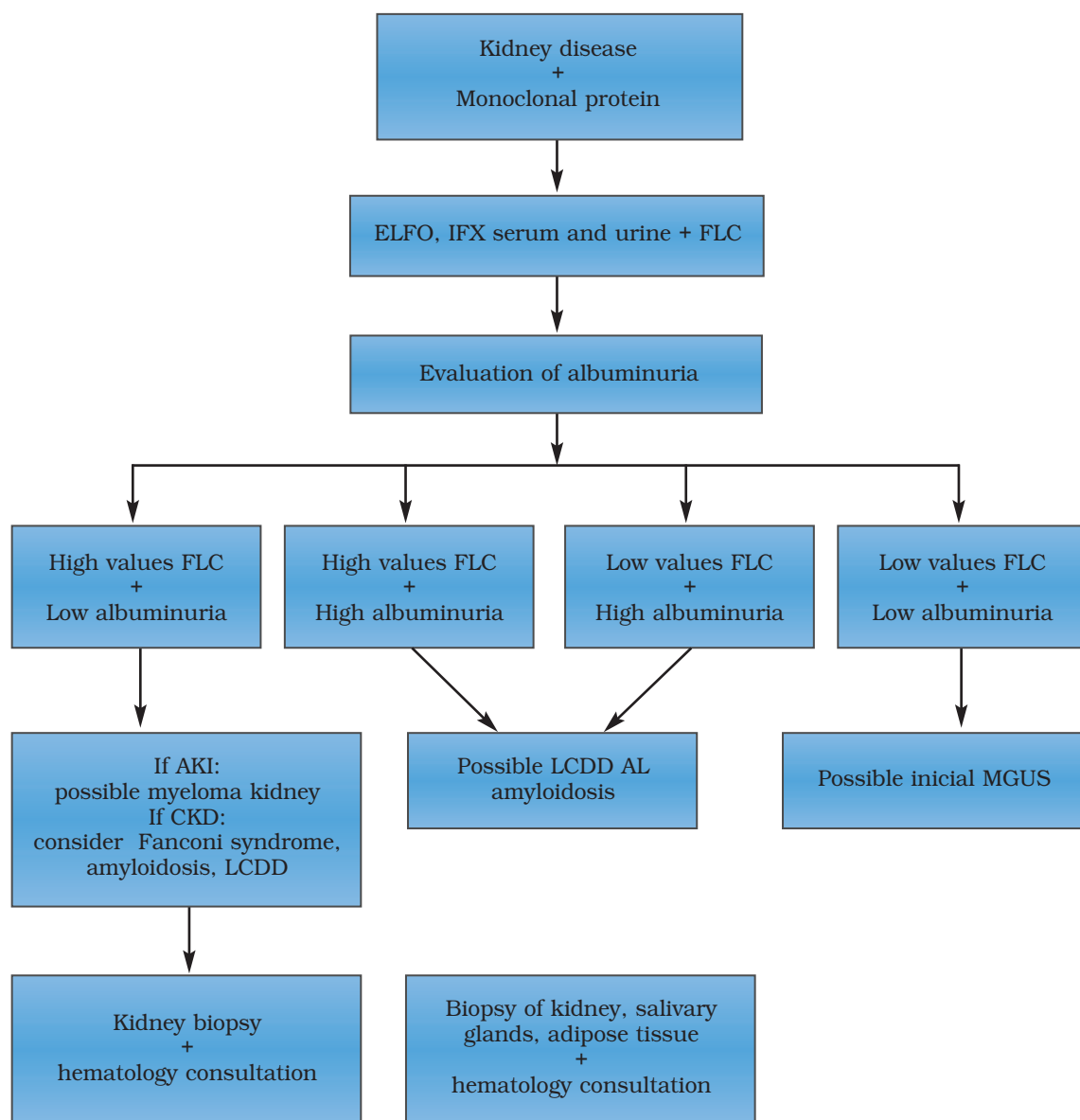
Diagnosis

As already mentioned, the clinical manifestations of MGRS are diverse and range from proteinuria to AKI to CKD with progression to terminal kidney failure (ESKD – an end-stage kidney disease) with the need to replace their function. Given the above, early detection of the cause with subsequent adequate therapy is extremely important. The algorithm showing MGRS screening in patients with AKI and CKD is shown in Figs. 1 and 2 (13).



AKI – acute kidney injury , ELFO – electroforesis, FLC – Free Light Chains, MG – monoclonal gam-mopathy

Fig. 1 Diagnostic algorithm for AKI (12)



CKD – chronic kidney disease, ELFO – electroforesis, IFX – immunofixation, FLC – Free Light Chains, AKI – acute kidney injury, LCDD – Light chain deposition disease, MGUS – monoclonal gamopathy of undetermined significance

Fig. 2 Diagnostic algorithm for CKD (12)

The most frequently used method for monoclonal protein detection is ELFO proteins, which can detect the M-gradient (paraprotein or its parts - light chains) from a concentration of 500 mg/l. A more sensitive methodology with the ability to detect paraprotein from 150 mg/l is represented by IFX of proteins in serum, where it is possible to determine the class of monoclonal immunoglobulin (IgG, IgM, and IgA) and the type of FLC – κ or λ using antisera. However, this method is labour-intensive and is therefore used for unclear findings

in ELFO, low-secretion forms of MG, AL amyloidosis, and for monitoring the treatment of patients when the paraprotein concentration drops below a value that cannot be measured by ELFO (13, 14).

In cases where the concentration of FLC reaches a value below 150 mg/l, the sensitivity of these two methods is inadequate, and the clinically relevant monoclonal FLC may not be detected. For the aforementioned reason, FLC detection was introduced into practice. The first test available on the market, currently included in international recommendations (e.g. IMWG – International Myeloma Working Group, IKMG and others) for MG diagnosis and treatment monitoring, is a susceptible turbidimetric and nephelometric test (Freelite®, Birmingham, UK). The sensitivity of the Freelite® test for kappa FLC is 0.6 mg/l and for lambda FLC it is 1.3 mg/l. Under physiological circumstances, the serum concentration of kappa chains is less than that of lambda chains due to their different molecular weight in favour of lambda chains (25:50 kDa). The assay uses rabbit antibodies directed against human FLC epitopes which are hidden in the case of intact immunoglobulin and exposed in the case of the free form of the light chain. In addition to quantifying each FLC isotope, it also provides information on the FLC ratio. The value of the κ/λ ratio depends on their formation by monoclonal plasma cells and the renal clearance value. Because the estimated glomerular filtration rate (eGFR – estimated glomerular filtration rate) is reduced in MGRS, modified reference values of the κ/λ ratio are shown in Table 2 (2, 13).

Table 2 Interpretation of the determination FLC (1,2)

Parameter	FLC kappa	FLC lambda	κ/λ ratio
Normal ratio	3,3 – 19,4 mg/l	5,5 – 26,3 mg/l	0,26 – 1,65
Monoclonal gammopathy	increased	normal/decreased	increased
Monoclonal gammopathy	normal/decreased	increased	decreased
Bi/oligoclonal diseases	increased	increased	varied*
Polyclonal diseases	increased	increased	normal
Renal injury	increased	increased	slightly increased
Reference values – nephrological patients**			0,46 – 2,62 (45 – 59) 0,48 – 3,38 (30 – 44) 0,54 – 3,30 (< 30)
Bone marrow suppression	decreased	decreased	normal
*depends on the concentration ratio of FLC ** specific reference value according eGFR			

FLC – Free Light Chains, eGFR – estimated glomerular filtration rate ml/min/m³

Other examination modalities include urine ELFO and IFX, which have significant disadvantages compared to serum FLC testing: 10 times less sensitivity and the need for inconvenient 24-hour urine collection, which often leads to patient non-cooperation. For the reasons above, we are increasingly meeting in professional discussions with the proposal to omit ELFO and IFX from urine from the diagnostic algorithm. However, according to the recommendations of the IMWG from 2009, it is necessary to perform immunofixation electrophoresis of 24-hour urine in correlation with the amount of FLC in the serum in all

patients with suspected MG, especially in MG associated with FLC formation (AL-amyloidosis, non-secretory myeloma, light chain myeloma) (6, 10).

In every patient with MG who develops AKI, a kidney biopsy with subsequent immuno-histochemical examination of the sample under light microscopy is required as part of the differential diagnosis; if available, it is also advisable to supplement the examination of the sample with an electron microscope. The classification of MGRS depends on the histopathological findings and the location of the nephron, as well as the type of kidney damage and the degree of the pathological process, which largely influence the aggressiveness of subsequent therapy. In the case of infiltration of the sample with monoclonal antibodies or when cast cylinders from light chains are found, it is MM with the need for immediate therapy. However, studies show that approximately half of patients with chronic kidney disease and concomitant MGUS did not have histologically verified MGRS. Therefore, early detection and quantification of the monoclonal protein is necessary, with an impact on the subsequent therapeutic management and prognosis of the patient with MGRS (4, 10, 13, 15).

Treatment

The treatment of MG correlates with the type of gammopathy, the differential diagnosis of which is shown in Table 3 (16).

Therapy for newly diagnosed patients with MM varies depending on the suitability of autologous stem cell transplantation (ASCT). Patients who are suitable for ASCT (eligible patients) undergo 3–4 cycles of chemotherapy with the VRd regimen (bortezomib, thalidomide/lenalidomide, and dexamethasone) or with the Dara-VRd regimen followed by ASCT. Patients unsuitable for ASCT (transplant ineligible patients) are treated with a VRd or DRd (daratumumab, lenalidomide, and dexamethasone) regimen for 8–12 cycles followed by maintenance therapy with lenalidomide or bortezomib (16).

The treatment of patients with MGRS is focused on monoclonal B-cells with chemotherapeutics, although there are no standardized guidelines. The goal is to preserve kidney function or to prevent recurrence after kidney transplantation, which can only be performed after the haematological remission of the disease has been achieved. In addition to targeted therapy, supportive therapy is also essential in terms of sufficient hydration (fluid intake > 3 l/day), elimination of nephrotoxic substances, treatment of hyperuricemia (diet/allopurinol), anaemia (erythropoiesis-stimulating preparations), antithrombotic prophylaxis (acetylsalicylic acid/low-molecular-weight heparin), vaccinations against influenza and pneumococci (17).

CONCLUSION

Although monoclonal gammopathy does not represent cancer in the true sense of the word, it significantly contributes to increased patient morbidity and mortality. An essential part of the differential diagnosis of sudden AKI is the suspicion of a haematological etiology. Including serum FLC detection tests in the first diagnostic line significantly improved the diagnosis of MG with the subsequent possibility of early therapy. The treatment of MG belongs to the hands of an experienced haematologist, but due to the involvement of other organs, it requires interdisciplinary cooperation.

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