THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

KIDNEY DISEASE IN MULTIPLE MYELOMA – CLINICAL FEATURES AND DIAGNOSIS

Camelia ACHIM[1], Andreea PANDELESCU[1], Eliza SIMSENSOHN[1], Anca ZGURA[2]

[1] Department of Nephrology, Fundeni Clinical Institute, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;
[2] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Correspondence to: Anca Zgura, "Carol Davila" University of Medicine and Pharmacy,
37 Dionisie Lupu Street, District 2, 020021 Bucharest, Romania. Tel: +40 751110005, e-mail: medicanca@gmail.com

Accepted

Multiple myeloma (MM) is a type of bone marrow cancer, a malignant proliferation of plama cells. The symptoms and signs of the disease are very divers. Fatigue and bone pain are the two, most common, symptoms at presentation. Anemia and kidney failure are complications of MM. Renal failure as acute kidney injury (AKI) or chronic kidney disease (CKD) is present in a high percentage of the patients with multiple myeloma. New insight in epidemiology, pathogenesis and clinical features of renal disease in multiple myeloma are review in this article.

Keywords:

INTRODUCTION

Multiple myeloma is a malignant proliferation of plasma cells derived from a single clone. Malignant myeloma cells produce large quantities of abnormal immunoglobulin, monoclonal protein or M protein. Host response to the malignant tumor and its products it result in a number of symptoms and organs dysfunction. Renal involvement in MM patients is often the first sign of the disease or will appeared during the evolution of the malignancy.

Kidney disease is an important and major predictor of overall prognosis of patients with multiple myeloma. In patients with tubule-interstitial and glomerular LCDD, who received treatment, the prognosis is good, but in patients with AL amyloidosis, in whom amyloid deposition continues and progress to renal failure in most cases, the prognosis is worse.[1, 2]

EPIDEMIOLOGY OF RENAL DISEASE IN THE MM PATIENT

At the time of diagnosis, 20%–50% of patients with multiple myeloma prove to have kidney failure – AKI or CKD. Severe renal insufficiency (serum creatinine > from 2.0 to 2.5 mg/dL) is found in 15 to 20% of cases[3, 5–8] (Table 1).

A retrospective study (from Jan 1974 – 2019) on 196 patients with multiple myeloma and renal impairment, showed that 70.4% of patients had renal involvement at the time of diagnosis of myeloma, with an average serum creatinine level of 686,42 umol/l and average renal survival of 4 months, 66,83% progressing to ESRD[9]. Another retrospective study using a population based registry of 1038 patients with new MM onset, 24,6% of them presented with renal impairment, of which 14,9 % required hemodialysis, and median survival time was 21 months in renal impaired patients vs not reached at 3 years for other patients ($p<0.01$). Excess mortality rates due to renal impairment were maximum in the first 6 months after diagnosis[10].

A vast number of newly diagnosed patients with MM have AKI at onset, but the prevalence remains unclear, depending on which definition is used: 30%, 20%, 15% at a serum creatinine level of 1.5, 2 or 2.3 mg/dl, respectively[6, 11, 12].

PATHOGENESIS AND CLINICAL FEATURES OF RENAL DISEASE IN THE MM PATIENT

Multiple myeloma is one of the most common hematologic malignancies, which determines a very wide spectrum of renal lesions, encompassing nearly all nephropathologic entities. The pathogenesis chain

begins with the overproduction of an abnormal Ig fragment, usually light chains, by a proliferating plasma cell clone in the bone marrow, and they are released in exces in the blood stream. Normal light chains are filtered by the glomerulus and reabsorbed in the proximal tubule by the megalin-cubulin receptor system (endocitosis and metabolisation). However, when there is an excess of light chains, the megalin cubulin receptor's capacity is overwhelmed, the fragments being released into the tubules.

The broad spectrum of abnormal light chains determines the diversity of nephropathologic injury, leading to various clinical presentations: AKI, CKD, overt proteinuria, tubular dysfunction. Not all the mechanisms that lead to renal failure in multiple myeloma are Ig-dependent, such as hypercalcemia, sepsis, tumor lysis syndrome, medication toxicity. However, the most common Ig dependent kidney disease in MM are cast nephropathy, monoclonal immunoglobulin deposition disease and AL amyloidosis (Table 2).

CAST NEPHROPATHY

The excess light chains production (also called Bence-Jones proteins), overcomes the capacity of the proximal tubular cells to absorb and catabolize, so FLCs arrive in the distal tubule where they precipitate and form tubular casts with Tamm-Horsfall protein, that lead to tubular obstruction. In this case, the clinical expression is acute kidney injury. Development of AKI is associated with poor 1-year survival and reduces the therapeutic options available to patients[13]. Early diagnosis and identifying the cause of AKI is essential for proper management and avoiding chronic kidney injury, which affects the patient quality of life and survival[14].

The obstruction by tubular casts triggers an inflammatory response, which leads to interstitial nephritis, followed by tubular atrophy and interstitial fibrosis. Atrophy and fibrosis are the pathologic basis of CKD in cast nephropathy[13]. Both lambda and kappa chains are involved (recent studies find no predominance[3,6,12]) and FLC>1g/dl are more likely to cause renal failure[6], which may evolve to CKD stage 3–5, including ESRD.

Factors that might contribute to myeloma cast nephropathy include the direct toxicity of Bence Jones proteins to tubular cells, protein complex formation in the distal nephron, tubular fluid pH, a reduction in RPF and GFR (dehydration, decreased urine flow), systemic electrolyte abnormalities, hypercalcemia, acidosis and loop diuretics[15, 16].

AL AMYLOIDOSIS

Al amyloidosis is found in 30% of patients with MM[17], and is the result of fibril formation, derived from Ig light chains or light chains fragments; these fibrils are made of polypeptide chains, which are perpendicular to the axis in a B-pleated sheet form. In the kidney, the fibrils deposit in the glomerulus and characteristically stain with Congo red, producing a green birefringence under polarized light. The MM patient with AL amyloidois has significant proteinuria (10–15 g/dL), 20% of patients have renal failure at the time of diagnosis and extrarenal involvement is frequent. The usual clinical outcome is CKD and ESRD.

Table 1

Frequency of kidney failure in MM patients

20–40% of newly diagnosed patients with MM	Alexanian *et al*, 1990; Blade *et al*, 1998; Kyle *et al*, 2003; Eleutherakis-Papaiakovou *et al*, 2007
creatinine level > 2 mg/dL – 20% of MM patients at diagnosis	Alexanian et al, 1990; Blade *et al*, 1998; Knudsen *et al*, 2000
creatinine level > 1,5mg/dL – 30–50% of MM patients at diagnosis	Knudsen *et al*, 2000
eGFR < 50 mL/min/1,73 m^2 and creatinine level < 4 mg/dL most of the patients	Torra *et al*, 1995
severe renal failure and need for renal replacement therapy – 10% of newly MM patients admitted in tertiary hospital	Torra *et al*, 1995
24,6% – renal insufficiency at diagnosis; 12,9% required hemodialysis	Courant M, 2021
renal failure developed later in the course of the disease – 25%	Kastritis E and Dimopoulos M, 2016

Table 2

Kidney disease in MM patients – pathogenesis and clinical features

Myeloma cast nephropathy " Myeloma kidney"	Acute: The excess light chains production overcomes the capacity of the proximal tubular cells to endocytosis and catabolize and FLCs precipitates in the distal tubule where they form tubular cats with Tamm-Horsfall protein that lead to tubular obstruction Chronic: tubular atrophy and interstitial fibrosis	AKI or recent onset of kidney failure Evolution to ESRD Evolution to CKD stage 3-5, including ESRD
Amyloidosis	Deposition of immunoglobulin in the form of amyloid fibrils al over the nephron; Red Congo positive	Significant proteinuria, nephrotic range: 10-15g/day Renal failure in 20% of the patients at diagnosis; evolution as CKD to ESRD Extra renal involvement frequent
Light chain deposits disease (LCDD)	Non-fibrilar light chain deposits; Red Congo negative; similar with membranoproliferatine gn type 2 or diabetic lesion	Nephrotic syndrome and rapidly impaired of renal function Extra renal involvement is less frequent than in amyloidosis
Heavy chain deposition disease (HCDD)	Heavy chain deposits in glomeruli and other structure	Proteinuria, non-nephrotic or nephrotic range Renal failure, evolution as CKD
Tubular dysfunction - Acquired Fanconi Syndrome	Due to tubular toxicity of light chains; failure in the reabsorptive capacity of the proximal renal tubule	Tubular proximal acidosis (Glycosuria, aminoaciduria, hypophosphatemia and hypouricaemia) Slowly progressive renal insufficiency Bone pain from osteoporosis

MIDD

Monoclonal IG deposition disease is a group of three disorders, named after the type of IG that determines them: LCDD – light chain deposition disease, HCDD – Heavy chain deposition disease and LHCDD – light and heavy chain deposition disease. MIDD accounts for a quarter of patients with MM as the cause of renal dysfunction. LCDD is the most common form. The deposits are non-fibrilar and red-Congo negative. Clinical features include nephritic syndrome and decline of renal function. Extrarenal involvement is less frequent than in AL amyloidosis. Overt myeloma is found in only 20% of LCDD patients[17]. The diagnosis of MIDD usually precedes the MM diagnosis in 70% of cases[18].

It is important to mention that some of the kidney lesions found in MM may coexist and can be detected on the renal biopsy, having a prognostic value. Cast nephropathy is found in 21% of MIDD cases; less often, amyloid can be seen on a MIDD patient's biopsy[18–20]. As in amyloidosis, extrarenal manifestations are frequent.

FANCONI SYNDROME

In multiple myeloma, FLCs can determine proximal tubular lesions. When they are reabsorbed in the proximal tubular cells, they undergo a homotypic polymerization within their endolysosomal system which leads to the formation of intracellular crystals, a pathologic characteristically feature for this syndrome. The FLCs are more often the kI subclass and the associated myeloma is usually low grade[21].

Clinical features reflect the impairment of proximal tubule function: type II tubular acidosis, glycosuria, phosphaturia and hypophosphatemia, aminoaciduria, hypouricemia. The decline in renal function is slowly progressive.

DIAGNOSIS AND ASSESSMENT OF RENAL DISEASE IN THE MM PATIENT

Renal impairment in the multiple myeloma patients must be evaluated in order to establish

wether the myeloma is the cause of the kidney disease, as the prognosis without treatment is grim. In a patient with AKI without established etiology, the nephrologist should always be alert for the diagnosis of MM.

DIAGNOSIS OF MM

Patients with MM present usually with hypercalcemia, anemia, renal failure and bone lesions (CRAB criteria). The active MM is preceded by an indolent phase called MGUS (monoclonal gamopathy of unknown significance). In MGUS, there is a monoclonal protein detected (< 3g/dL) but there is no end organ damage[22]. The intermediate condition between MGUS and symptomatic MM is called smouldering or indolent myeloma.

The initial symptoms are often non-specific, like weight loss, fatigue, malaise, bone pain. Anemia is very specific and it's found in 75% of patients. As CKD often presents with non-specific symptoms and anemia, anemic patients with renal impairment should always be screened for paraprotein disease.

Patients with MIDD or amyloidosis often have extrarenal involvement, thus having systemic symptoms at presentation such as heart failure, arrhythmias, gastro-intestinal bleeding, elevated alkaline phosphatase and periorbital purpura[23].

The International Myeloma Working Group consensus agreed to include validated biomarkers to the definition of MM, in addition to the CRAB criteria: *Calcium: serum calcium >0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL); Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >1.77 mol/L (>2 mg/dL); Anemia: hemoglobin value of >2 g/dL below the lowest limit of normal, or a hemoglobin value <10 g/dL; Bone lesions: osteolytic lesions on skeletal radiography, CT, or PET/CT.* This update includes certain biomarkers, *clonal bone marrow plasma cells greater than or equal to 60%, serum free light chain (FLC) ratio greater than or equal to 100 provided involved FLC level is 100 mg/L or higher, or more than one focal lesion on MRI*, which have been found to associate with the imminent development of CRAB features in patients with smouldering myeloma and aloud to diagnose myeloma in patients without CRAB features[24] (Table 3).

DETECTION OF THE MONOCLONAL IG

The gold standard for diagnosis and detection of monoclonal Ig has been protein electrophoresis, but, unfortunately, it has very low sensitivity for free light chains and cannot differentiate monoclonal from polyclonal on regular basis[2]. The most recent test for monoclonal Ig detection is FLC immunoassay, which can detect monomers and dimmers of k and lambda chains at a concentration of less than 2–4 mg/L, with or without the concomitant presence of intact monoclonal Ig[25]. The FLC immunoassay does not detect clonality by itsown, but rather is suggesting it through abnormal values of k/l ratio. One of the advantages of FLC assay is its increased diagnostic sensitivity: a vast number of patients with AL, non-secretory myeloma or MIDD with no monoclonal ig detected in usual testing, will have abnormal k/lambda ratios[2, 26, 27]. However, the k/lambda ratio interpretation is altered in patients with CKD. In a retrospective analysis, including patients with no hematologic disease, patients with MM in complete remission and with active MM, all of the groups having patient with CKD, the influence of eGFR on the sFLC ratio interpretation is confirmed. There is a decreased specificity in advanced CKD stages, especially in patients with eGFR < 55 mL/min. Authors suggest a modified k/L optimal range (0.82–3.6) for eGFR < 55 ml/min[28].

DIAGNOSIS OF RENAL IMPAIRMENT

The organ criterion for kidney damage as agreed by the International Myeloma Working Group (IMWG), is defined by a serum creatinine concentration (sCr) > 2 mg/dL or eGFR < 40 mL/min. Patients with multiple myeloma can present with very fast deterioration of their renal function –acute kidney injury, most common in cast nephropathy and hypercalcemia, or with slow deterioration over time – chronic kidney disease. Some patients will have severe AKI at presentation, often fulminant and dialysis dependent. Hypercalcemia, dehydration, nephrotoxic agents, may contribute to the rapid decrease in renal function.[29]

Table 3

Kidney disease in MM patients – pathogenesis

Kidney failure related to: – Hypercalcemia – Hypervascozity – Hyperuricemia – Other risk factors for KF in MM patients: – nephrotoxic drugs (antibiotics, NSAIDs, contrast agents)	Accelerated bone resorbtion High concentration of clonal Ig Tubular precipitation of uric acid due to tumoral lisis	AKI
Membranoproliferative GN		Crioglobulins deposition
Pyelonephritis/ Sepsis		AKI
Other comorbidities not related with MM, especially in older patients: AH, diabetes mellitus	Hypertensive nephropathy Diabetic nephropathy	Microalbuminuria to nephrotic syndrome; CKD

Assessment and diagnosis of AKI in MM using eGFR was criticized because it is used for definition and staging of CKD, but not yet proven accurate for AKI. The RIFFLE criteria used for the staging of AKI have not yet been validated for MM patients. However, a 15 year retrospective study used the RIFFLE criteria to stage the severity of AKI, which predicted renal response and was associated with marginally better long-term outcome, concluding that RIFFLE criteria may have a role in early prevention and management of AKI.[30]

Assessment and diagnosis of CKD in MM starting with definition of CKD, as abnormalities of kidney structure or function, present for 3 months, with implications for health: Albuminuria (AER ≥ 30 mg/24 hours; ACR ≥ 30 mg/g [≥ 3 mg/mmol]), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by kidney biopsy, structural abnormalities detected by imaging, history of kidney transplantation and/or GFR < 60 mL/min/1.73 m^2 (GFR categories G3a–G5)[31] (Table 4).

Accurate assessment of glomerular filtration rate in patients with multiple myeloma is very important for renal function evaluation, risk stratification, prognosis and drug dosing. The formula used for assessment of renal function and eGFR is important, since the value of serum creatinine alone can overestimate the renal function, especially in older patients with multiple comorbidities and low muscle mass. A large analysis on 1937 patients with symptomatic MM treated in centers of the Greek Myeloma study group evaluated the prognostic significance of renal function assessed by two different formulas: CKD-EPI and MDRD and found that eGFR calculated by the CKD-EPI formula changes the stage of CKD in about 9% of patients and has better prognostic value for survival and predicts early death more accurately than the MDRD formula[32]. The situation may differ for patients with MM who received ASCT treatment, as shown in a long term study which evaluated the impact of sCr and eGFR calculated by the MDRD formula on overall survival. They used a lower treshold than IMWG criteria (sCr > 1.4 mg/dL, eGFR < 5 mL/min) and showed that even slightly increased sCr and decreased eGFR, which are not meeting the IMWG criteria, require effort to reverse even minimal renal impairment, taken into consideration the negative correlation between minimal renal insufficiency and long term outcome.[29]

The CKD-EPI group suggested a higher accuracy of eGFR based on both sCr and Cystatine C (CKD-EPI-sCr-CysC) than other formulae such as MDRD. The Greek Myeloma Study Group made a prospective evaluation on renal function on newly diagnosed patients with symptomatic MM, using CKD-EPI-sCr-CysC and found that it reveals a higher number of patients with renal impairment. The CysC formula also predicted survival independently[33] (Table 5).

NGAL (neutrophil gelatinase-associated lipocalin) is a relatively recent discovered biomarker of kidney damage. A series of 199 patients with MM were studied with results indicating that plasma NGAL is a sensitive biomarker, levels correlated significantly with renal damage degree as defined by KDIGO, and with the sCr, CysC concentration and eGFR. NGAL also proved to be a possible marker to reflect tumor burden in patients with MM[34].

The assessment of the amount and type of proteinuria in the 24-hour urine collection is essential in the evaluation process of the MM patient with kidney disease. Urine dipsticks detect albumin only and are unreliable. In cast nephropathy (no glomerular lesion), FLCs (Bence-Jones proteins) will predominate in the urine. Urine immune electrophoresis will show a large spike in the gamma-region and urine immuno-fixation will show free kappa or lambda light chains. The 24-hour urine proteins will be less than 25% albumin. When it comes to glomerular lesions (amyloidosis, LCDD or other preexisting renal diseases: diabetic nephropathy, hypertensive nephropathy), 24-hour urine analysis will show non-selective proteinuria with predomination of albumin.

Kidney biopsy is essential in MM patients with nephrotic syndrome or non-nephrotic non-selective proteinuria, with or without renal failure, with low FLCs serum levels, without overt myeloma or with pre-existing renal dysfunction. In this case, renal biopsy is necessary to prove associated systemic amyloidosis or LCDD (glomerular lesion), or unrelated glomerulopathy or glomerular lesions associated with other pre-existing disease (diabetic nephropathy or hypertensive nephropathy in elder patients)[35]. However, MM patient with light chains proteinuria, with or without renal failure, with small amount of albumin and mainly light chains, > 200mg/day and serum FLCs > 500mg/L, renal biopsy could not be necessary as the cause of renal impairment may be atributed to cast nephropathy (tubular lesions)[36].

CONCLUSIONS

Kidney disease is a major complication in patients with MM. Knowledge of epidemiology, better understanding in pathogenesis and clinical features of renal disease in MM patients and collaboration between multiple specializations as hematology, nephrology, lab medicine goes to a better diagnosis and management of these patients. A large variety of clinical features of renal disease as impairment of renal disease, acutely due to cast nephropathy or chronically due to AL amiloidosis, proteinuria as nephritic syndrome in MIDD or Fanconi syndrome is present in MM patients. Diagnosis of renal disease in MM patients must include diagnosis of MM, detection of monoclonal Ig and diagnosis of renal impairment. AKI, using RIFLE criteria and CKD, using CKD EPI sCr or better sCr – CysC formula must be provided as diagnosis of renal impairment. Kidney biopsy remain "gold standard" diagnosis in MM patients with nephrotic syndrome or non-nephrotic, non-selective proteinuria, with or without renal insufficiency, with low FLCs serum levels, without overt myeloma or with pre-existing renal dysfunction due to other condition (arterial hypertension, diabetes mellitus or other glomerulopathy, non-related with MM.

REFERENCES

1. Ludwig, H., Novis Durie, S., Meckl, A., Hinke, A. and Durie, B. (2020), Multiple Myeloma Incidence and Mortality Around the Globe; Interrelations Between Health Access and Quality, Economic Resources, and Patient Empowerment. The Oncol, 25: e1406-e1413. https://doi.org/10.1634/theoncologist.2020-0141.
2. Eliot C. Heher, Helmut G. Rennke, Jacob P. Laubach, Paul G. Richardson: Kidney disease and multiple myeloma. CJASN Jul 2013, CJN.12231212; DOI: 10.2215/CJN.12231212.
3. Knudsen LM, Hjorth M, Hippe E: Renal failure in multiple myeloma: Reversibility and impact on the prognosis. Nordic Myeloma Study Group. Eur J Haematol 65 : 175–181, 2000.
4. Haynes RJ, Read S, Collins GP, Darby SC, Winearls CG : Presentation and survival of patients with severe acute kidney injury and multiple myeloma: A 20-year experience from a single centre. Nephrol Dial Transplant 25: 419–426, 2010pmid:19767634.
5. Pešić, Snezana & Grujic, Nevena & Stopić, Bojan & Jankovic, Aleksandar & Markovic, Katarina & Damjanovic, Tatjana & Naumovic, Radomir. (2021). MO222DO WE OFTEN THINK OF MULTIPLE MYELOMA AS THE CAUSE OF KIDNEY DISEASE?. Nephrology Dialysis Transplantation. 36. 10.1093/ndt/gfab092.00100.
6. Knudsen LM, Hippe E, Hjorth M, Holmberg E, Westin J: Renal function in newly diagnosed multiple myeloma: A demographic study of 1353 patients. The Nordic Myeloma Study Group. Eur J Haematol 53 : 207–212, 1994.
7. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR: Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 78 : 21–33, 2003.
8. Blade J, San Miguel JF, Fontanillas M, Esteve J, Maldonado J, Alcala A, Brunet S, Garcia-Conde J, Besalduch J, Moro MJ, Fernandez-Calvo J, Conde E, Font L, Gardella S, Carnero M, Carbonell F, Marti JM, Hernandez-Martin J, Ortega F, Besses C, Ribera JM, Trujillo J, Escudero ML, Rozman C, Estape J, Montserrat E: Increased conventional chemotherapy does not improve survival in multiple myeloma: Long-term results of two PETHEMA trials including 914 patients. Hematol J 2 : 272–278, 2001.

9. Nessrine Breik, Barbouch Samia, Mariem Najjar, Safa Fattoum, Sawsen Ben Nsira, Seif Azaiez, Amel Harzallah, Syrine Karoui, Imen Gorsane, Fethi Benhmida, Monther Ounissi, Taieb Benabdallah, P0332. Diagnostic, therapeutic and Evolutionary Features of Kidney Disease in Multiple Myeloma, Nephrology Dialysis Transplantation, Volume 35, Issue Supplement_3, June 2020, gfaa142.P0332, https://doi.org/10.1093/ndt/gfaa142.P0332
10. Maxime Courant, Sebastien Orazio, Alain Monnereau, Julie Preterre, Christian Combe, Claire Rigothier, Incidence, prognostic impact and clinical outcomes of renal impairment in patients with multiple myeloma: a population-based registry, Nephrology Dialysis Transplantation, Volume 36, Issue 3, March 2021, Pages 482–490, https://doi.org/10.1093/ndt/gfz211
11. Dimopoulos MA, Sonneveld P, Leung N, *et al.* International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol. 2016;34:1544–1557.
12. Bladé J, Fernández-Llama P, Bosch F, *et al.* Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. Arch Intern Med. 1998;158:1889–1893.
13. Finkel KW, Cohen EP, Shirali A, Abudayyeh A; American Society of Nephrology Onco-Nephrology Forum. Paraprotein-Related Kidney Disease: Evaluation and Treatment of Myeloma Cast Nephropathy. Clin J Am Soc Nephrol. 2016 Dec 7;11(12):2273-2279. doi: 10.2215/CJN.01640216. Epub 2016 Aug 15. PMID: 27526708; PMCID: PMC5142056.
14. Bridoux F, Leung N, Belmouaz M, Royal V, Ronco P, Nasr SH, Fermand JP; International Kidney and Monoclonal Gammopathy Research Group. Management of acute kidney injury in symptomatic multiple myeloma. Kidney Int. 2021 Mar;99(3):570-580. doi: 10.1016/j.kint.2020.11.010. Epub 2021 Jan 10. PMID: 33440212.
15. Kastritis E and Dimopoulos M, Chapter 153: "The patient with myeloma" in Oxford Textbook of Nephrology, vol 2, Fourth Edition, 2016, pag 1276.
16. Kyle RA, Greipp PR: Amyloidosis (AL): Clinical and laboratory features in 229 cases. Mayo Clin Proc 58 : 665–683, 1983.
17. Hogan JJ, Alexander MP, Leung N. Dysproteinemia and the Kidney: Core Curriculum 2019. Am J Kidney Dis. 2019 Dec;74(6):822-836. doi: 10.1053/j.ajkd.2019.04.029. Epub 2019 Jul 19. PMID: 31331759.
18. Lin J, Markowitz GS, Valeri AM, Kambham N, Sherman WH, Appel GB, D'Agati VD: Renal monoclonal immunoglobulin deposition disease: The disease spectrum. J Am Soc Nephrol 12 : 1482–1492, 2001.
19. Gallo GR, Lazowski P, Kumar A, Vidal R, Baldwin DS, Buxbaum JN: Renal and cardiac manifestations of B-cell dyscrasias with nonamyloidotic monoclonal light chain and light and heavy chain deposit in diseases. Adv Nephrol 28 : 355–382, 1998.
20. Paueksakon P, Revelo MP, Horn RG, Shappell S, Fogo AB: Monoclonal gammopathy: Significance and possible causality in renal disease. Am J Kidney Dis 42 : 87–95, 2003.
21. Paul W. Sanders, Mechanisms of Light Chain Injury along the Tubular Nephron, JASN November 2012, 23 (11) 1777-1781; DOI: https://doi.org/10.1681/ASN.2012040388.
22. Douglas E Joshua, Christian Bryant, Caroline Dix, John Gibson, Joy Ho: Biology and therapy of multiple myeloma, Med J Aust 2019; 210 (8): . || doi: 10.5694/mja2.50129.
23. Pozzi C, D'Amico M, Fogazzi GB, Curioni S, Ferrario F,Pasquali S, Quattrocchio G, Rollino C, Segagni S, Locatelli F: Light chain deposition disease with renal involvement: Clinical characteristics and prognostic factors. Am J Kidney Dis 42: 1154–1163, 2003pmid:14655186.
24. S. Vincet Rajkumar. Updated Diagnostic Criteria and Staging System for Multiple Myeloma. Am Soc Clin Oncol Educ Book. 2016; 35:e418-23.
25. Maldonado JE, Velosa JA, Kyle RA, Wagoner RD, Holley KE, Salassa RM: Fanconi syndrome in adults. A manifestation of a latent form of myeloma. Am J Med 58 : 354–364, 1975.
26. Sanders PW, Herrera GA: Monoclonal immunoglobulin light chain-related renal diseases. Semin Nephrol 13 : 324–341, 1993/
27. Deret S, Denoroy L, Lamarine M, Vidal R, Mougenot B, Frangione B, Stevens FJ, Ronco PM, Aucouturier P: Kappa light chain-associated Fanconi's syndrome: Molecular analysis of monoclonal immunoglobulin light chains from patients with and without intracellular crystals. Protein Eng 12 : 363–369, 1999/
28. Molina-Andújar, A., Robles, P., Cibeira, M.T. *et al.* The renal range of the κ/λ sFLC ratio: best strategy to evaluate multiple myeloma in patients with chronic kidney disease. BMC Nephrol 21, 111 (2020). https://doi.org/10.1186/s12882-020-01771-3/
29. Waszczuk-Gajda A, Małyszko J, Vesole DH, Feliksbrot-Bratosiewicz M, Skwierawska K, Krzanowska K, Kobylińska K, Biecek P, Snarski E, Rodziewicz-Lurzyńska A, Kozłowski P, Stefaniak A, Drozd-Sokołowska J, Ziarkiewicz M, Vyas P, Boguradzki P, Mądry K, Biliński J, Tomaszewska A, Maciejewska M, Urbanowska E, Blajer B, Król M, Król M, Zborowska H, Jurczyszyn A, Dwilewicz-Trojaczek J, Jedrzejczak WW, Basak GW. Negative Impact of Borderline Creatinine Concentration and Glomerular Filtration Rate at Baseline on the Outcome of Patients With Multiple Myeloma Treated With Autologous Stem Cell Transplant. Transplant Proc. 2020 Sep;52(7):2186-2192. doi: 10.1016/j.transproceed.2020.02.067. Epub 2020 Mar 26. PMID: 32222395.
30. Shi H, Zhang W, Li X, Ren H, Pan X, Chen N. Application of RIFLE criteria in patients with multiple myeloma with acute kidney injury: a 15-year retrospective, single center, cohort study. Leuk Lymphoma. 2014 May;55(5):1076-82. doi: 10.3109/10428194.2013.820284. Epub 2013 Aug 20. PMID: 23865828.
31. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements, 2013, 3.
32. Meletios A. Dimopolous, Evanghelos Terpos *et. al,* Estimated Glomerular Filtration Rate Calculated By The CKD-EPI Formula Has Improved Prognostic Ability Over MDRD Formula In Patients With Newly Diagnosed, Symptomatic, Multiple Myeloma: Analysis In 1937 Patients, November 2013, Blood 122(21):1867-1867, DOI:10.1182/blood.V122.21.1867.1867, Project: Greek Myeloma Study Group.

33. Terpos E, Christoulas D, Kastritis E, Katodritou E, Pouli A, Michalis E, Papassotiriou I, Dimopoulos MA; Greek Myeloma Study Group. The Chronic Kidney Disease Epidemiology Collaboration cystatin C (CKD-EPI-CysC) equation has an independent prognostic value for overall survival in newly diagnosed patients with symptomatic multiple myeloma; is it time to change from MDRD to CKD-EPI-CysC equations? Eur J Haematol. 2013 Oct;91(4):347-55. doi: 10.1111/ejh.12164. Epub 2013 Aug 17. PMID: 23829647.
34. Chae H, Ryu H, Cha K, Kim M, Kim Y, Min CK. Neutrophil gelatinase-associated lipocalin as a biomarker of renal impairment in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk. 2015 Jan;15(1):35-40. doi: 10.1016/j.clml.2014.07.014. Epub 2014 Aug 1. PMID: 25204517.
35. Giampaolo Merlini, Giovanni Palladini; Differential diagnosis of monoclonal gammopathy of undetermined significance. Hematology Am Soc Hematol Educ Program 2012; 2012 (1): 595–603. doi: https://doi.org/10.1182/asheducation.V2012.1.595.3798563.
36. Samih H.Nasr, Anthony M.Valeri, Sanjeev Sethi, Mary E.Fidler, Lynn D.Cornell, Morie A.Gertz, Martha Lacy, Angela Dispenzieri, S. Vincent Rajkumar, Robert A. Kyle, Nelson Leung. Clinicopathologic Correlations in Multiple Myeloma: A Case Series of 190 Patients With Kidney Biopsies; AJKD Volume 59, Issue 6, June 2012, Pages 786-794; doi.org/10.1053/j.ajkd.2011.12.028.