Light Chain Nephropathy

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Introduction

- Acute kidney injury (AKI) is a common complication in symptomatic multiple myeloma (MM)

- light chain cast nephropathy (LCCN) is the most frequent cause.

Myeloma light chain cast nephropathy, a review

Insara Jaffer Sathick[1] · Maria Eleni Drosou[2] · Nelson Leung[2,3]

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- Renal impairment is a serious complication during the course of the disease that is associated with **increased morbidity and mortality**

Background

- up to 40% of patients have a serum creatinine above the upper normal of limit **at diagnosis** with 10% requiring dialysis
- Is associated with **higher tumor burden** and **poor prognosis**
- End stage renal disease (ESRD) due to MM carries a worse prognosis than ESRD of other causes with an almost three-fold increase in mortality risk in the first year of renal replacement therapy (RRT)

Journal of Nephrology
https://doi.org/10.1007/s40620-018-0492-4

Renal impairment in MM

✓**Autopsy studies** on 57 patients with MM demonstrated that:

- Cast nephropathy in 32%
- AL amyloidosis in 11%
- Light chain deposition disease (LCDD) in 5%

Ivanyi B (1990) Frequency of light chain deposition nephropathy

Renal impairment in MM

Less commonly:

- Proliferative glomerulonephritis
- Thrombotic microangiopathy
- Fibrillary glomerulonephritis
- Cryoglobulinemia and Pyelonephritis
- Focal Segmental Glomerulosclerosis
- Plasma cell infiltration
- Renal extramedullary hematopoiesis and
- Crystalline podocytopathy

Ivanyi B (1990) Frequency of light chain deposition nephropathy

Nephrol Dial Transplant (2016) 31: 64–72
doi: 10.1093/ndt/gfv283
Advance Access publication 19 August 2015

ndt
Nephrology Dialysis Transplantation

Original Article

Prognostic value of kidney biopsy in myeloma cast nephropathy: a retrospective study of 70 patients

- Of 72 renal Bx, pure LCCN was diagnosed in 41, while 4 had another nephropathy coexisting with LCCN.
- Around 25% of patients had another light chain (LC)–induced renal disease, including AL amyloidosis (n 12), LC deposition disease (n 6), or Fanconi syndrome (n 1).
- Finally, 8 patients had kidney lesions unrelated to MM, 6 of whom with vascular atherosclerotic renal disease

Diagnostic approach

- **Renal impairment**:
- **Acute** (cast nephropathy)
- **Subacute** : progressive rise in creatinine over a period longer than 6 months more common in other renal pathologies such as AL amyloidosis, MIDD

Epidemiology

- The second most common hematologic malignant neoplasm
- Slightly more common in men
- Increases risk with age
- Acute or chronic renal impairment is thought to occur in **half** of patients during the course of the disease
- In a study that used the **RIFLE** (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria, 35% of patients with MM had AKI with 5% staged as risk, 5% as injury, and 25% as failure

Application of RIFLE criteria in patients with multiple myeloma with acute kidney injury

Renal impairment in MM

- light chain cast nephropathy is almost always occurs with a serum monoclonal (M) spike of > 3 g/dL or clonal plasma cells of > 10% in bone marrow and other myeloma features.
- Most of the other lesions are currently classified Monoclonal Gammopathy of Renal Significance (MGRS)
- Unless have CRAB (hypercalcemia, Renal Impairment, Anemia and Bone lesions)

Journal of Nephrology
https://doi.org/10.1007/s40620-018-0492-4

Pathogenesis of light chain-induced tubular injury in MM

- Free light chain (FLC) is the **nephrotoxic component** of the aberrant circulating monoclonal protein in MM.
- Physiologically, 500 mg polyclonal free light chains (FLCs) are produced daily
- Under normal conditions, FLCs are cleared from the circulation by the kidneys with a half-life of about 3–6 h
- In the context of renal failure as would be seen in cast nephropathy, the half-life increases to 2–3 days, resulting in injury to the surviving nephrons

Pathogenesis and Presentation of Light Chain Cast Nephropathy

- **kappa** and **lambda** light chains have binding site for the THP
- There is a direct relationship between the **risk of cast nephropathy** and the **serum concentration of FLC**
- The risk of AKI is proportional to the daily excretion of Bence Jones protein
- In FLC overproduction, like in MM, the receptor mediated transport system becomes saturated.

Curr Hematol Malig Rep (2018) 13:220–226

Pathogenesis and Presentation of Light Chain Cast Nephropathy

- FLCs exert **direct toxic effects** to the **proximal tubular** epithelial cells
- THGP/FLC trigger **inflammation** with leukocyte recruitment, reactive oxygen species and cytokine release, and multiple kinase activation
- Interstitial peritubular inflammatory infiltrates are common in LCCN, and tubular cell apoptosis/necrosis initiate a process of rapid **scarring of the renal parenchyma**

International Journal of Nephrology and Renovascular Disease 2022:15 173–183

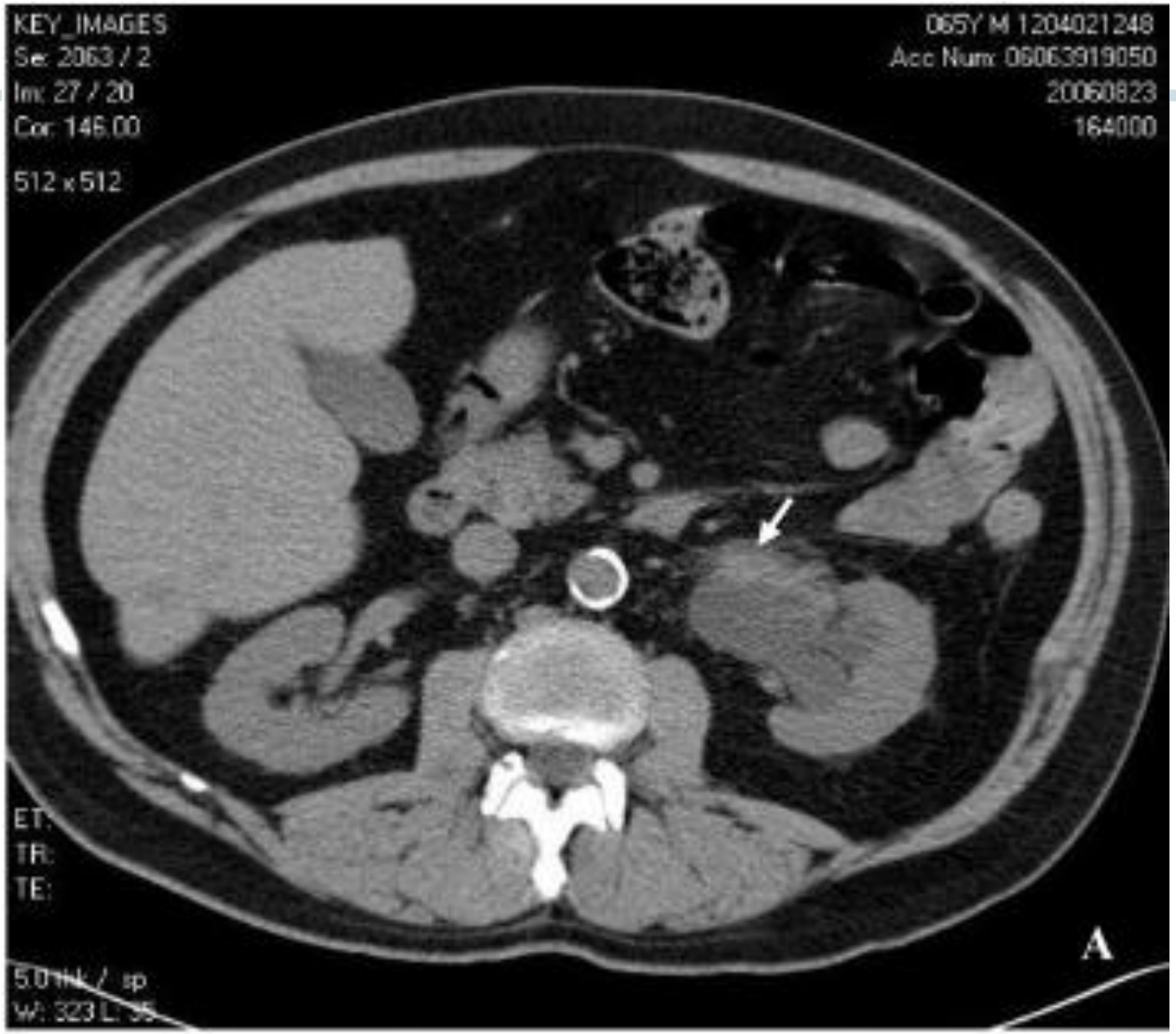
Spectrum of renal impairment in symptomatic MM

- Renal complications **not related** to MIg

- **Obstruction of the urinary tract** due to bladder or ureteral extramedullary **plasmocytoma** and renal parenchymal plasma cell infiltration are uncommon

Kidney International (2021) 99, 570–580

- CT scan revealed an obstructive retroperitoneal tumour infiltrating the left ureter and renal pelvis and responsible for ureterohydronephrosis.
- A transparietal biopsy of the tumour showed a proliferation of large plasmablastic cells that stained positive for CD138



NDT Plus (2009) 2: 143–146

Renal complications **not related** to MIg

- **Hypercalcemia** is present in 15% of patients with MM at presentation, but the prevalence is 2- to 3-fold higher (25%–45%) in those with an elevated serum creatinine level
- Hypercalcemia may induce **Prerenal AKI** by dehydration and vasoconstriction, and it is a common precipitating factor of LCCN
- **Infections** such as septicemia, pneumonia, pyelonephritis may cause AKI
- **Prerenal AKI** due to NSAIDS ,Diuretics, ACEIs and trigger of cast formation

Kidney International (2021) 99, 570–580

Renal complications **not related** to MIg

- AKI **after treatment** such as zolendronic acid
- **Renal thrombotic microangiopathy** is a potential complication of proteasome inhibitors, particularly **carfilzomib**.
- Lenalidomide has been associated with acute reversible non-LC–related **Fanconi syndrome**
- **Tumor lysis syndrome**, very unusual in the past, is increasingly described at the initiation of chemotherapy, particularly in patients with altered renal function

Kidney International (2021) 99, 570–580

Renal complications **related to MIg**

- Deposition or precipitation of the entire MIg or a fragment (usually the monoclonal LC).
- Monoclonal Gammopathy of Renal Significance
- Monoclonal immunoglobulin deposition diseases (MIDDs)
- Monoclonal LC can also injure proximal tubules causing **Fanconi syndrome**
- Glomerulopathies with deposits of C3 only
- Thrombotic microangiopathy

Kidney International (2021) 99, 570–580

Clinical presentation

The clinical presentation of these disorders ranges from sub–nephrotic-range **proteinuria** or microscopic hematuria with preserved kidney function to severe nephrotic syndrome to severe acute kidney injury or rapidly progressive glomerulonephritis

Clinical presentation

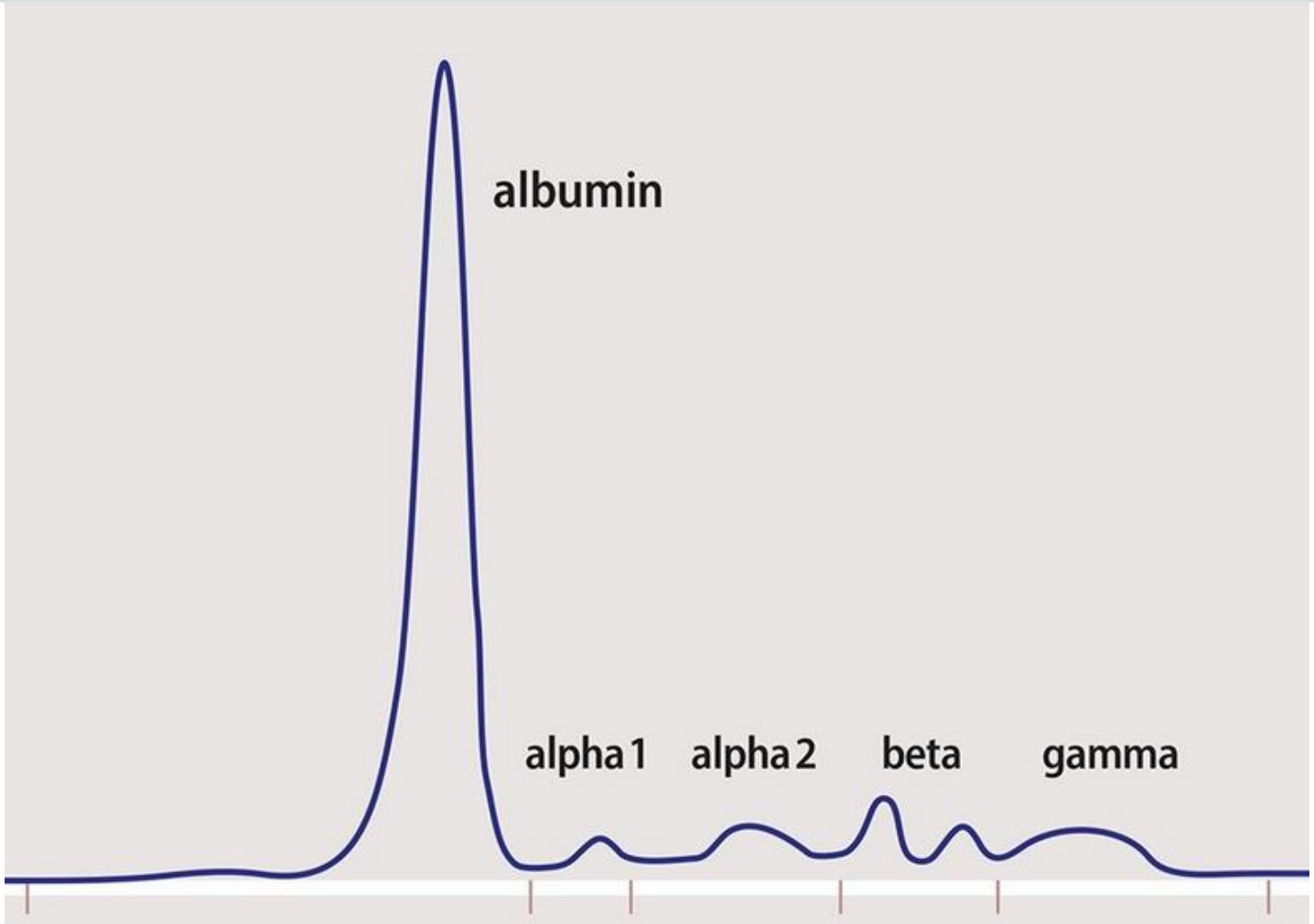
- **AKI of unknown origin**, particularly in the elderly and when other MM manifestations are missing, it is crucial to consider LCCN
- Initial diagnostic workup is **serum and urinary protein electrophoresis** and measurement of **sFLC levels**

Clinical presentation

perform a bone marrow examination if:

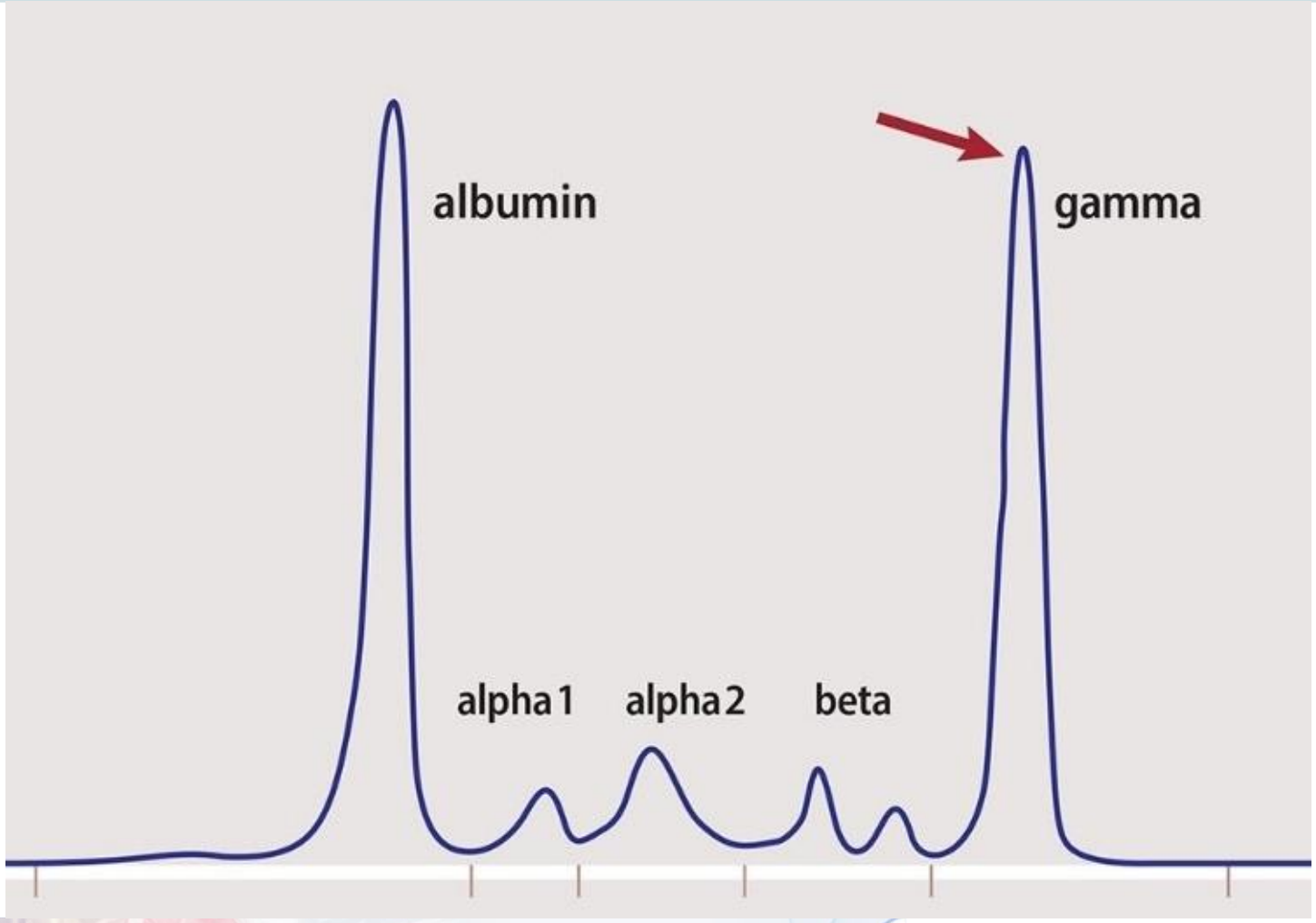
- A monoclonal spike or
- Hypogammaglobulinemia
- Urinary albumin/protein ratio of <10%, and/or
- Significantly increased level of one LC isotype
- Abnormal kappa/lambda ratio

Serum and Urine Protein Electrophoresis (SPEP and UPEP)



The International Myeloma Foundation

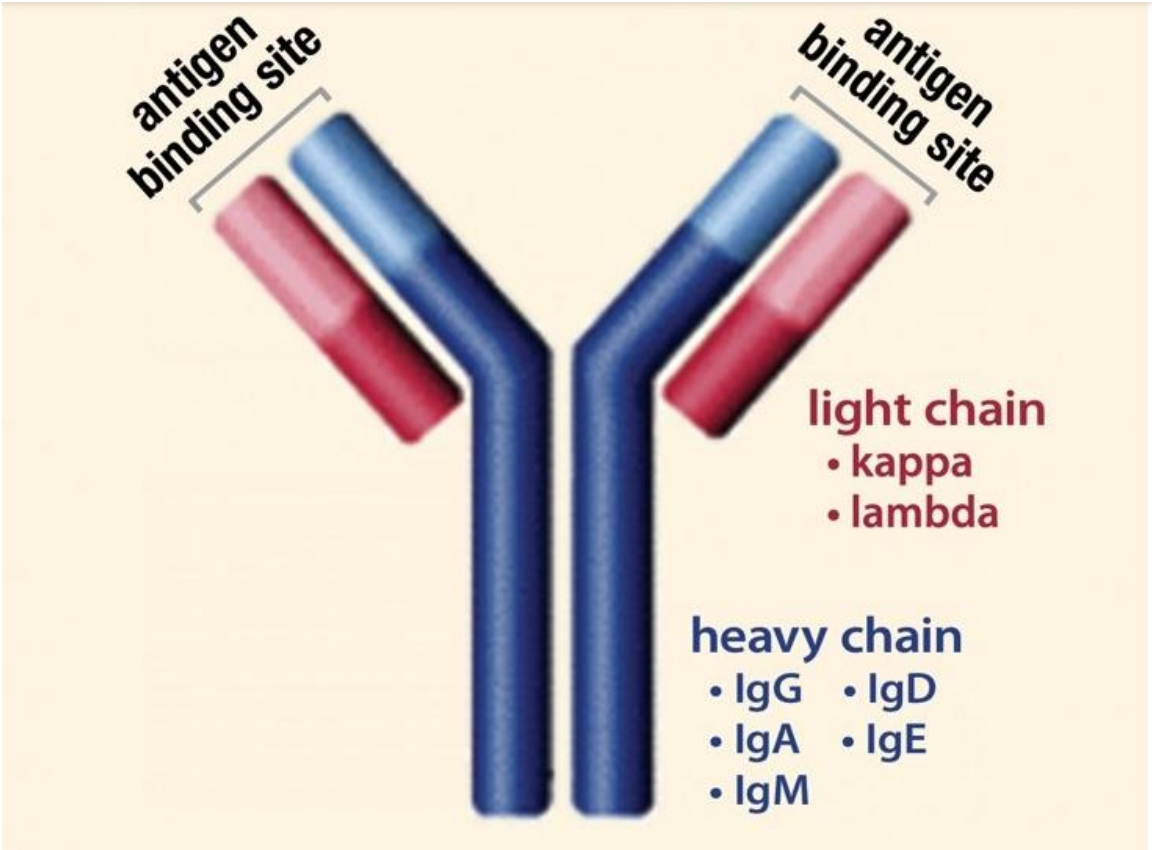
SPEP in MM



The International Myeloma Foundation

Serum Free Light Chain

For unknown reasons, the plasma cells produce more light chains than heavy chains. The excess, or unbound, light chains circulate freely in the blood. Hence, they are called “free” light chains.



The International Myeloma Foundation

Sensitivity of Serum Paraprotein Testing for Multiple Myeloma, Smoldering Myeloma, and AL Amyloidosis

	Multiple Myeloma	Smoldering Multiple Myeloma	AL Amyloidosis
SPEP	87.6%	94.2%	65.9%
Serum IFE	94.4%	98.4%	73.8%
Serum FLC assay	96.8%	81.2%	88.3%
SPEP and serum FLC	100%	99.5%	94.2%
SPEP, serum IFE, and serum FLC assay	100%	100%	97.1%

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Prognostic Value of SFLC

- An abnormal kappa/lambda ratio is a nonspecific finding and indicates a **state of chronic inflammation**
- An abnormal kappa/lambda ratio suggests an adverse outcome in a nonspecific way as do elevated ferritin, CRP, and RDW, and lower levels of serum albumin
- In patients with no MIg, an abnormal kappa/lambda ratio indicates a **worse prognosis**

November 2020 | 05:06 | 1358–1371 | JALM

Monitoring the Results of Treatment

light chains have a shorter **half-life** than Ig, so **changes in SFLCs** could be used to ascertain response or lack of re-sponse to treatment faster than using level of neoplastic MIg

JALM | 1358–1371 | 05:06 | November 2020

Factors Precipitating Light Chain Cast Nephropathy (LCCN)

Heavy FLC filtered load (high concentration of paraproteins in tubular luminal fluids)

Dehydration, high-dose diuretics (low tubular flow following initial diuresis)

Hypercalcemia (through polyuria and dehydration)

Hyperviscosity syndrome

Nephrotoxic drugs

- Nonsteroidal anti-inflammatory drugs
- Aminoglycoside antibiotics
- Bisphosphonates (zoledronate, alendronate)

Radiologic contrast media

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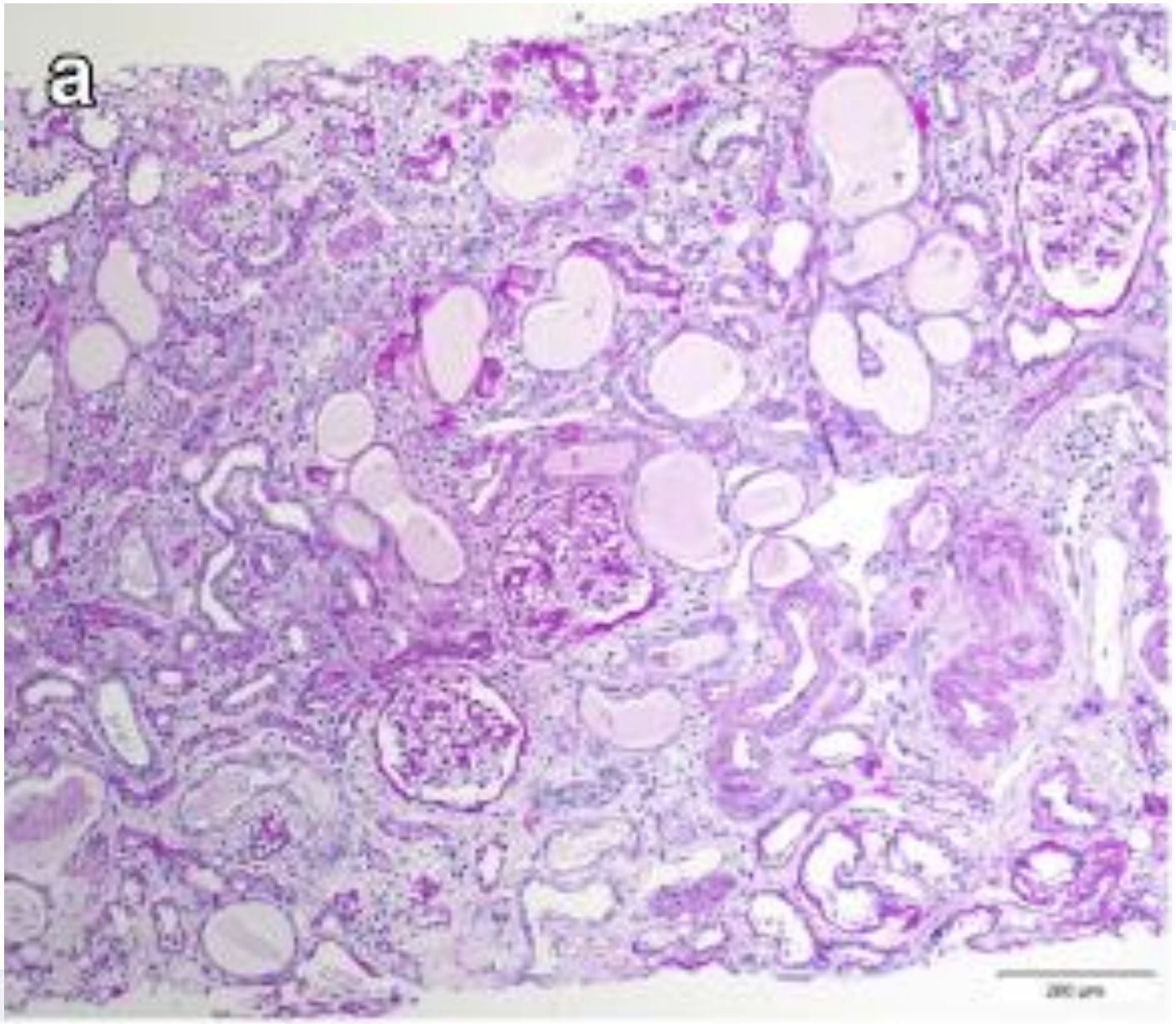
blood®
Volume 135, Issue 21, 21 May 2020, Pages 1833-1846

CME Article

Clinicopathologic predictors of renal outcomes in light chain cast nephropathy: a multicenter retrospective study

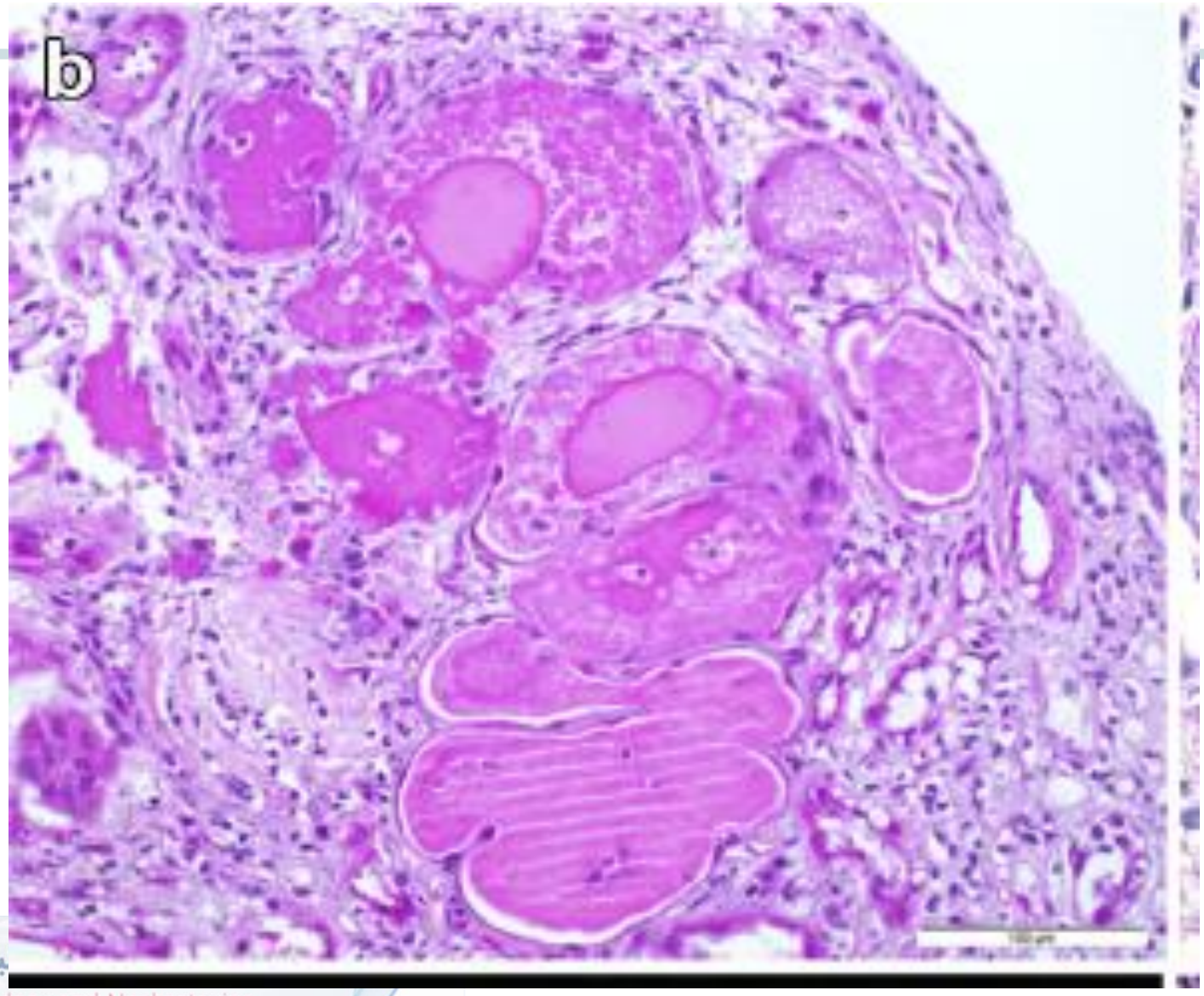
In a retrospective study of 178 patients with MM and LCCN, of whom 47% required dialysis at presentation, the **number of casts** per millimeter square in the cortex and the degree of **interstitial fibrosis/tubular atrophy** were independent **prognostic factors** of renal outcome.

Numerous (PAS)–negative cortical casts associated interstitial fibrosis and tubular atrophy



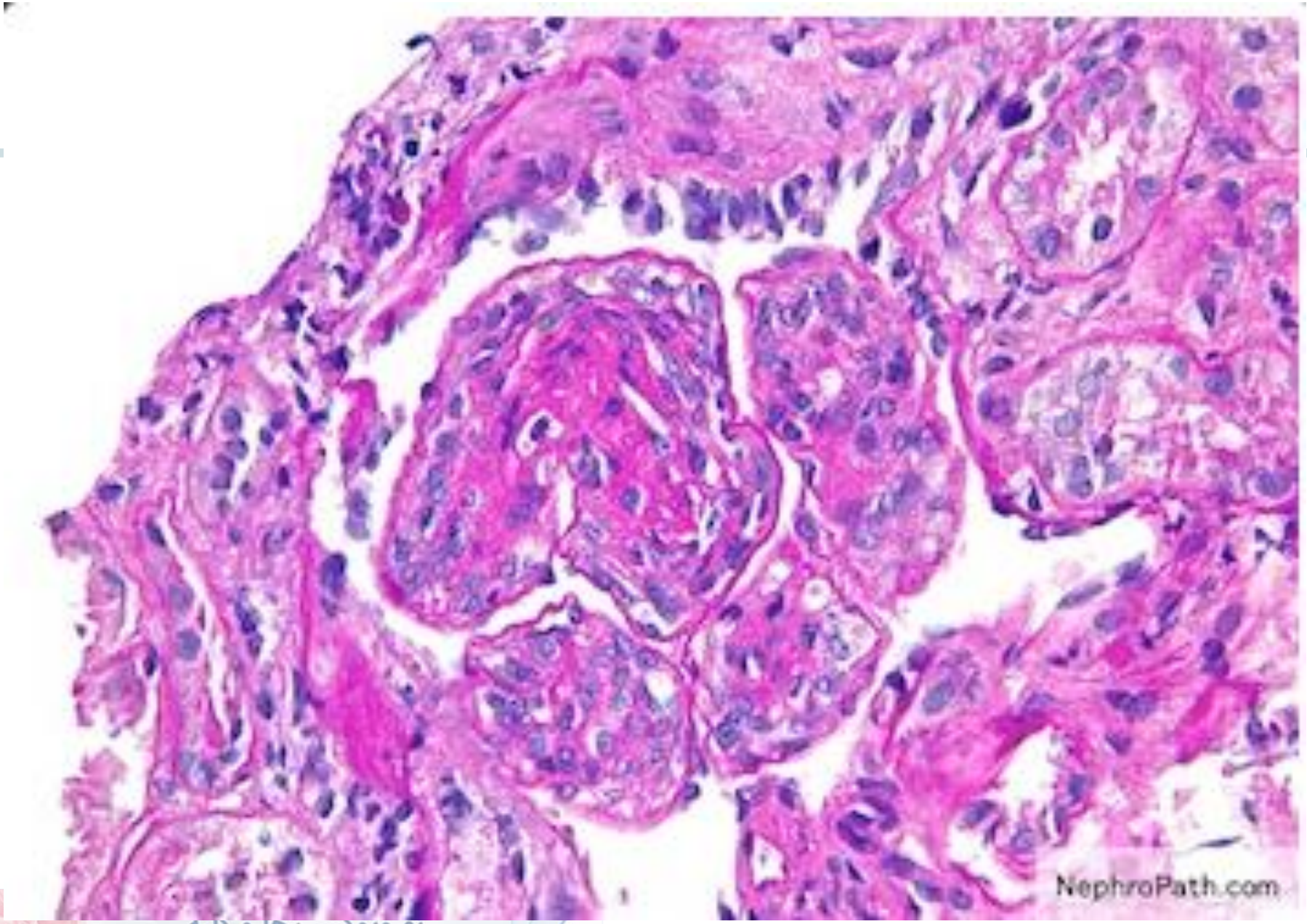
F Bridoux et al.: Management of AKI in myeloma

Intraluminal hypereosinophilic casts distending the tubules, resulting in tubular ruptures (hematoxylin and eosin)



F Bridoux et al.: Management of AKI in myeloma

Light chain deposits along GBM



Pathology

In 12% to 16% of cases, LCCN may coexist with other MIg-related kidney lesions, particularly AL amyloidosis,classical LC deposition disease, and LC proximal tubulopathy.

Yadav et al. *Blood Cancer Journal* (2020)10:28
https://doi.org/10.1038/s41408-020-0295-4

Blood Cancer Journal

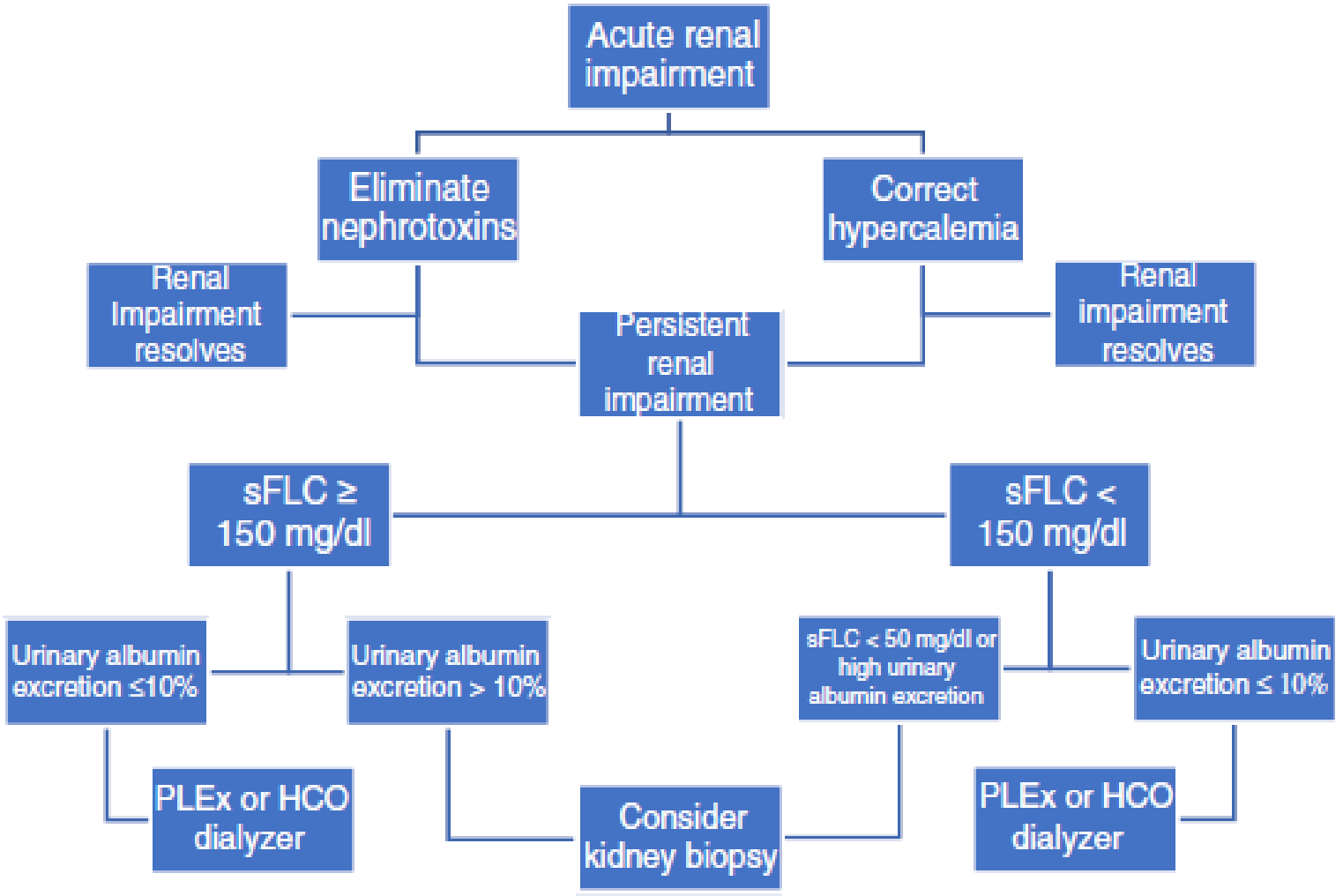
ARTICLE Open Access

Serum free light chain level at diagnosis in myeloma cast nephropathy—a multicentre study

Punit Yadav[1,2], Insara Jaffer Sathick[3], Nelson Leung[3], Elizabeth E. Brown[4], Mark Cook[5], Paul W. Sanders[6,7] and Paul Cockwell[1,2]

- In any patient with **MM** who presents with or develops **renal insufficiency**, the combination of low urinary albumin excretion (urinary albumin/total protein ratio <10% and urinary albumin/creatinine <30 mg/mmol) and high sFLC level (>500 mg/l) strongly argues for the diagnosis of LCCN and systematic **histological confirmation is not required**

Approach to patients with suspected cast nephropathy



Curr Hematol Malig Rep (2018) 13:220–226

Treatment of precipitating factors

- **Volume repletion** to achieve a urine output of > 3 l/day
- Nephrotoxic medications (NSAIDs, ACEIs, ARBs) should be discontinued
- Zoledronate and pamidronate
- Denosumab, a monoclonal antibody that inhibits the osteoclast-mediated bone resorption
- Glucocorticosteroids, treatment of hypercalcemia and also effective in rapid reduction of paraprotein production.

Kidney International (2021) 99, 570–580

Chemotherapy

- Goal of therapy is the **decrease of FLC production**
- The phase II study by Ludwig et al. on 68 patients with MM presenting with AKI showed that treatment with the bortezomib dexamethasone-doxorubicin regimen led to myeloma response of 72% and renal response of 62%

Ludwig H, J Clin Oncol 28(30):4635

Chemotherapy

- Comparison between the **PAD** (bortezomib doxorubicin dexamethasone) and the vincristine, doxorubicin-dexamethasone (**VAD**) regimens followed by autologous stem cell transplantation (SCT)
- Subgroup analysis found that the use of **PAD was superior** both in terms of progression free survival and OS compared to VAD in the renally impaired patients
- **Cyclophosphamide** was recently shown to be noninferior and also less toxic compared to doxorubicin as a third agent

J Clin Oncol 30(24):2946–2955

Chemotherapy

- **Thalidomide**, also not requiring dose reduction, has been found to **increase OS** when added to the bortezomib
- **Lenalidomide** should be avoided in patients with AKI due to its nephrotoxic potential and the need for dose reduction due to renal clearance

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice–Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue

Joseph Schwartz, Anand Padmanabhan, Nicole Aqui, Rasheed A. Balogun, Laura Connelly-Smith, Meghan Delaney, Nancy M. Dunbar, Volker Witt, Yanyun Wu, Beth H. Shaz

First published: 20 June 2016 | https://doi.org/10.1002/jca.21470 | Citations: 334

- The benefit of **extracorporeal FLC removal** in patients with AKI has not been established
- MCN is a Grade 2B recommendation for therapeutic apheresis according to current guidelines of the American Society of Apheresis

J

J Am Soc Nephrol. 2007 Mar;18(3):886-95. doi: 10.1681/ASN.2006080821. Epub 2007 Jan 17.

Efficient removal of immunoglobulin free light chains by hemodialysis for multiple myeloma: in vitro and in vivo studies

- **Plasma exchange** might remove only 25% of the total amount during a 3-wk period
- Serum FLC reduced by 35 to 70% within 2 hr by **extended hemodialysis** but reduction rates slowed as extravascular re-equilibration occurred.

review www.kidney-international.org

Management of acute kidney injury in symptomatic multiple myeloma

Frank Bridoux[1,2,3], Nelson Leung[4,5], Mohamed Belmouaz[1,2], Virginie Royal[6], Pierre Ronco[7,8], Samih H. Nasr[9] and Jean Paul Fermand[10,11]; for the International Kidney and Monoclonal Gammopathy Research Group

- In patients with light chain cast nephropathy and acute kidney injury requiring dialysis, the combination of chemotherapy with free light chain removal through **High Cutoff Hemodialysis** may increase renal response recovery rates


Thank you