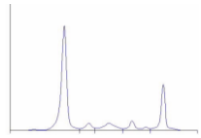
Plasma cell dyscrasia and renal diseases

Pathophysiology, diagnosis, clinical management, complications

Prof. Dr. P. Zachée
Internist Nefroloog & Hematoloog

Case 1



Men, 60j
28/9/2011:
No complains.

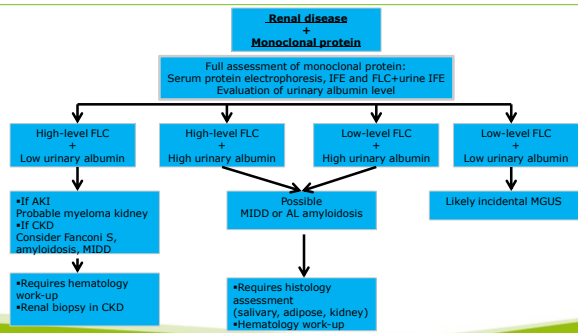
Physical examination: hypertension

Laboratory:
- Increase of the paraproteïne level

paraproteine pike: 1,94 g/dl
-> bone marrow: plasmocytosis 8%
- **creatinine 1,25 mg/dl** (eGFR: 59 ml/min)

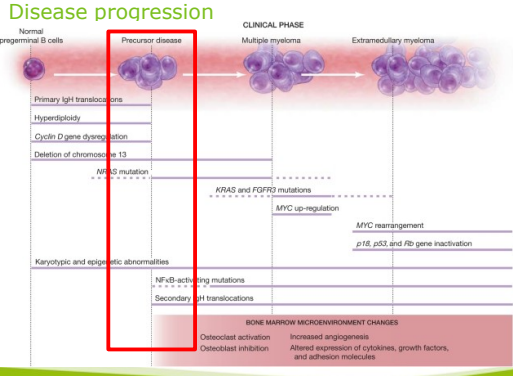
24 hour urine collection: **4,21 g/24 uur**
urine sediment: hematuria **dysmorfe rode bloedcellen**

Diagnostic approach to a patient with renal failure and a Mig



Hutchinson C.A.: Nat. Rev. Nephrol. 2012, vol 8 No; 43-51

Disease progression



Monoclonal gammopathy of renal significance
MGRS
Dangerous small B-cell clone

- MGRS are due to deposition of Mig fragments with distinct localization and pattern of ultrastructural organization
  - Organized deposits
    - Fibrillar
      - AL (amyloidosis : light chain)
      - AH (amyloidosis : heavy chain)
      - ALH (amyloidosis : light and heavy chain)
    - Microtubular
      - Type I and II cryoglobulinemia
      - ITG: immunotactoid glomerulopathy
  - Nonorganized deposits
    - Randall type monoclonal immunoglobulin deposition disease (MIDD)
    - Non Randall type proliferative glomerulonephritis with monoclonal deposits (PGNMID)
  - Tubular
    - Fanconi syndrome

Coexist

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Clinic & APO & Deposits

	AL AH ALH	Randall MIID	Type I Cryo	Type I Cryo	ITG	PGNMID	FS
Underlying disorder	Low grade plasma cell clone AL: λ > κ AH / ALH	>10% bone marrow plasma cells (MM) : K > λ	Single Mig RA factor: neg MGUS MM WM lymphoma	IgM K + polyclonal ig RA factor pos Hepatitis C B Auto-immune Sjögren B-cell clone -> WM lymphoma	CLL Small L L (plasma cell clone)	Frequent no detectable Mig Only in 30%	K MGUS Smouldering MM (WM)
Clinic Renal	36% proteinuria in the nephrotic range	proteinuria +++ Hematuria Hypertension RF	IgG > IgM Nephritic S Chronic RF Hypertension	Nephritic S Chronic RF Hypertension	Proteinuria Nephrotic S Hematuria, RF Hypertension	CKD	CKD 1-3 Urine loss: Phos, glucose,aminoacids RTA type 2
Extra renal manifestations	70 % Cardiac involvement & prognose	Rare	Tumor related	Vasculitis Arthralgia Peripheral neuropathy	Rare	Rare	Osteomalacia Other rare (crystal store histiocytosis)
APO	Renal biopsy is not mandatory if Other organ +	Nodular Glomerulo - sclerosis	MPGN Mig Glomerular trombi	MPGN Mig +Poli ig Glomerular trombi	Membranous/ MPGN Mig IgG +complement	Mesangial /Membranous/ MPGN Mig IgG3κ	Proxymal tubular cells desquamation fragmentation
Deposits	Fibrillar	Non organised Linear amorphic deposits	Organised Microtubular deposits	Organised Microtubular deposits	Organised Microtubular Deposits 10-60nm //	Non organised Linear amorphic granular deposits	Proximal tubules intracytoplasma crystalline & Fibrillar inclusions

Mig: monoclonal immunoglobulin, MM: muliple Myeloma, WM: Waldenström, LL: lymphocytic lymphoma
MGUS: monoclonal gammopathy of unkwon significance
MPGN: membranoproliferative glomerulonephritis. RTA: renal tubular acidosis

Miscellaneous

- POEMS
  - Polyneuropthy
  - Organomegaly: Enlarged spleen, liver or lymph nodes
  - Endocrinopathy: hypothyroidism, diabetes, sexual problems
  - M-protein
  - Skin abnormalities: more color than normal on your skin, possibly thicker skin and increased facial or leg hair, with nail

  - *Renal manifestations: vascular and thrombotic mocroangiopathy including mesangiolysis*
  - *Etiology VGE production by the clonal population*
  - *Treatment HDM/ASCT*

- Glomerulonefritis with isolated C3 deposits

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Miscellaneous

- POEMS

- Glomerulonefritis with isolated C3 deposits
  - Glomerolonephritis with C3 deposits
  - Mig IgG
  - Auto-antibody against a complement alternative pathway regulatory protein: hypocomplementia (due to the activation of the alternative pathway) and absence of a detectable anti-C3 convertase (nephritic factor)
  - Chemotherapy
  - High risk of recurrence in transplant kidney

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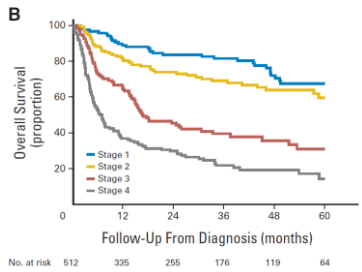
MAYO CLASSIFICATION for Amyloidosis pro-BNP & troponin T & FLC

Pro-BNP	≥ 1,800 pg/ml
Troponin T	≥ 0,025 ng/ml
FLC	≥ 18 mg/dl

Stage	Score
I	0
II	1
III	2
IV	3



A positive troponin I was virtually 100% specific and 100% predictive for a future cardiac event i. Yet its negative predictive value was only 50%. Cardiac troponin T is 100% sensitive in detecting dialysis patients who would have future cardiac events, with a negative predictive value of 100%.

Kumar: JCO 2012, 30(9): 989-995

TREATMENT of MGRS

Mayo stage	AL AH ALH	CKD	Randall MIDD	Type I Cryo	Type II Cryo	ITG	PGNMID	FS
Stage I	*CBD + HDM/ASCT in selected patients*	CKD 1	Slow Progression *CBD*	Plasmacytic IgG & IgA *CBOR CTD*	HCV Few symptoms *Antiviral treatment* More symptoms *+ rituximab*	*Cy & Benda +Corticosteroids*	Proteinuria < 1g/d *Wait and see* (spontanous remissions) Proteinuria >1g/d *CBD+Young patients HDM/ASCT*	Slow progression *Take into acount treatment side effects (MDS)* *CBD Thalidomide Bendamustine* *If no respons HDM/ASCT* *•Prevention of osteomalcia* Candidate RT *Chemotherapy HDM/ASCT* No Candidate RT *conservative*
Stage II	*CTD*	CKD 2	*+ HDM/ASCT (if no extra renal disease and if PR on CBD)*	Lympho-plasmacytic IgM Rituximab	No HCV *rituximab* WM / lymphoma *Rituximab Benda*	If overt CLL *+ rituximab*		
Stage III		CKD 3		CLL & B-lymphoma			*CBD* Young patients *HDM/ASCT*	
Stage IV	*CBD* In young patients cardiac transplantation after hematological remission +anti CD38 +others	CKD 4	Candidate RT *3&4 X CBD + HDM/ASCT* No Candidate RT *CBD*	*CLL lymphoma therapy Benda*	*+ plasma Exchange + steroids*	If gammopathy only *BD*	Candidate RT *HDM/ASCT* If no MIG or clonal disease ? No Candidate RT *conservative*	
		CKD 5						

CBD/CBOR: cyclofosfamide/ Bortezomib/Dexa
HDM/ASCT: high dose melphalen/autologous temcell transplantation
CTD: cyclofosfalide/thalidomide/dexa. BD: bortezomib dexamethasone
Benda: bendamustine, Cy: cyclofosfamide
HCV: hepatitis C, CLL: chronic lymfatic leukemia, RT: renal transplantation

9 Ozna

CYBorD

Treatment

Cyclophosphamide 300 mg/m^2 orally weekly)

Bortezomib 1.5 mg/m^2 weekly (IV & SC)

Dexamethasone 40 mg weekly

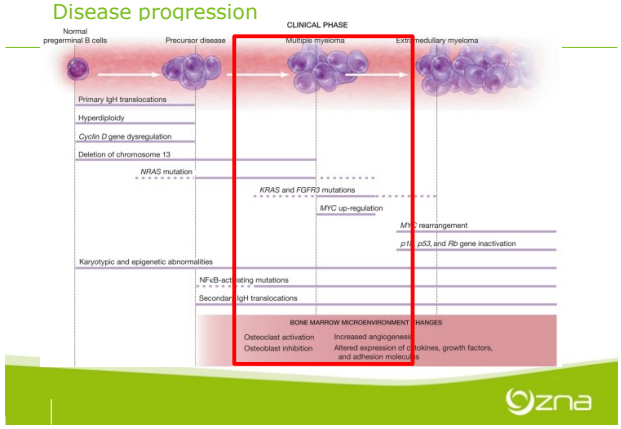
All patients were given antiviral prophylaxis.

MGRS What have we learned?

- Survival of MGRS is better than multiple myeloma but renal outcome are not (exception AL amyloidosis with cardiac involvement)
- In patients with MGRS look for
  - Characteristics of the monoclonal gammopathy
  - Is there an overt lymphoid or plasmacytic disorder
  - Search for extra renal manifestations
  - Kidney biopsy (IF and EM) (exception AL)
- When end-stage renal disease occurs MGRS should not be a contraindication to renal transplantation because the risk of patients dying from their clone is low. The decision for renal transplantation should be taken considering the underlying MGRS characteristics (AL slow recurrence, PGNMID rapid recurrence), initial therapeutic response, presence of extra renal manifestations, and patient status. Post renal transplantation careful surveillance of Mig and reintroduction of clonal therapy is mandatory.

Ozna

Disease progression



Case 2 Jos 66 years

- **2009 MGUS**
  - IgG-kappa :20,3 g/l
  - free κ: 97,7, free λ: 14,5 mg/l, κ/λ:6,74
  - Bone marrow: 5% plasmacellen. Flowcytometry: 10,6% plasma cells: CD38+HD/CD138+/CD56-.
  - No skeletal lesions

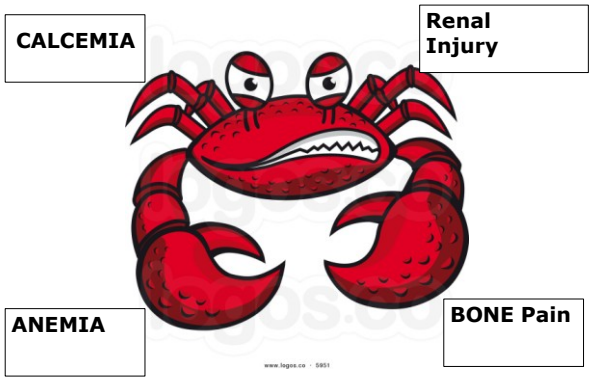
High Intermediate risk: control every 6 months

Follow-up of a MGUS

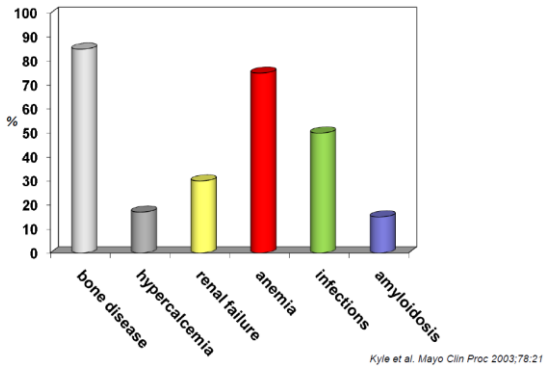
Risk-stratification models to predict progression of MGUS to MM or related disorders

Risico groep	Relatief risico	Absoluut risico voor progressie na 20 jaar	Absoluut risico voor progressie na 20 jaar, rekening houdend met overlijden als competitief risico
Laag risico (serum M proteïne < 1.5 mg/dl, IgG subtype, normaal FLC ratio (0.26 – 1.65)	**1**	**5%**	**2%**
Laag intermediair risico (1 factor abnormaal)	**5.4**	**21%**	**10%**
Hoog intermediair risico (2 factoren abnormaal)	**10.1**	**37%**	**18%**
Hoog risico (alle 3 de factoren abnormaal)	**20.8**	**58%**	**27%**

CRAB Symptoms

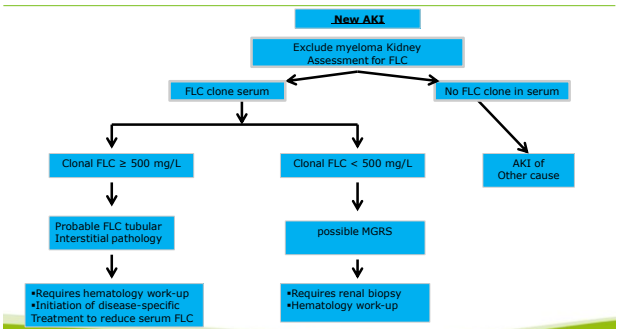


CRAB criteria for symptomatic Myeloma



Kyle et al. Mayo Clin Proc 2003;78:21

Diagnostic approach to a patient with Mig and AKI

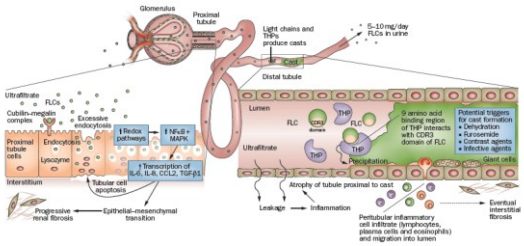


Hutchinson C.A.: Nat. Rev. Nephrol. 2012, vol 8 No; 43-51

Acute Kidney Injury in MM

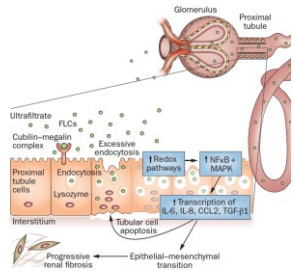
- In 1970 Survival of patients with AKI and MM was 2 months in comparison with 3 years in MM without AKI. Recently it was 10 months instead of 8,5 years
- In normal situation 500 mg polyclonal FLC which are produced daily by our lymphoid system is catabolized by the proximal tubule. Only 10 mg of polyclonal FLCs appear in the urine
- In plasma cell dyscrasia monoclonal FLC production is increased by > X 100. The capacity of the multiligand endocytic receptor complex is quickly exceeded. FLC appears in the tubular fluid = Bence Jones protein.
- Monoclonal FLC induces proximal tubular injury, cast nephropathy or both.
- FLC interact with the proximal tubule cell -> inflammation -> interstitial fibrosis.
- FLC interact with tamm-Horsfall (uromodulin) proteins -> cast formation ->block the flow -> tubular atrophy -> interstitial fibrosis.

Acute Kidney Injury in Multiple Myeloma



Proximal tubule injury **Distal tubule injury**

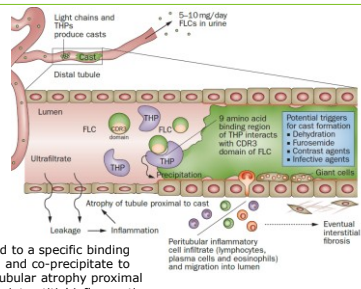
Proximal Tubule injury



The very high concentrations of FLCs present in the ultrafiltrate of patients with multiple myeloma can result in direct injury to PTCs. The excessive endocytosis of FLCs by the cubilin–megalin complex expressed on PTCs can trigger apoptotic, proinflammatory and fibrotic pathways. Activation of redox pathways occurs, with increased expression of NFκB and MAPK, which in turn leads to the transcription of both inflammatory and profibrotic cytokines, such as IL-6, IL-8, CCL2 and TGF-β1.

Hutchinson C.A.: Nat. Rev. Nephrol. 2012, vol 8 No; 43-51

Distal tubule injury (Cast nephropathy)



In the distal tubules, FLCs can bind to a specific binding domain on Tamm-Horsfall protein and co-precipitate to form casts. These casts result in tubular atrophy proximal to the cast and lead to progressive interstitial inflammation and fibrosis.

Hutchinson C.A.: Nat. Rev. Nephrol. 2012, vol 8 No; 43-51

Nephrotoxic potential of BJ Proteins

- **Conclusions**

A Particular Light chain is primary responsible for producing of distinctive types of protein deposition in renal tissue and the clinical manifestations that occur in patients with light-chain associated diseases. (rienfusion study of Light chain from patients in mouse)

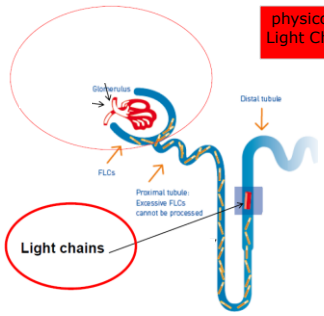
FLC proteinuria > 2g/d → AKI (V domain & related to pathology)

- **Casts**
- **Light-chain depostions (basament membrane)**
- **Crystals**
- **Amyloid**

- Renal biopsy is mandatory to determine the lesion. This is important concerning later renal transplantation.
- Nephrotoxicity is related to the light chain. Be aware for FLC escape in patients with intact Ig (5% in IgG en 15% in in IgA)

Solomon A: New Engl J Med 1991, vol 324, No 26

Etiology of Multiple Myeloma



physicochemical properties of the Light Chain (v)

Hypercalcemia
Hyperviscosity (total protein > 100 mg/dl)
Hyperuricemia

Infection
Dehydration
Contrast
Medication:
NSAID
Aminoglocosides

Treatment goals

restoration of the kidney function
anti-myeloma therapy

- Hydration + monitoring van de fluid balance
- Correction of the hypercalcaemia
  - Biphosphonates (adaptation to the Cr clearance)
- Avoid the use of van nefrotoxic medication and Contrast
- Rapid institution of quick-acting and efficient anti-myeloma
- Others
  - Plasmapheresis (if hyperviscosity)
  - Hemodialysis
  - Medium cut off dialysis to remove the FLC

Bladé et al. Arch Intern Med 1998;158:1889
Dimopoulos et al. J Clin Oncol 2009;27:6068

Quick-acting High efficient Anti Multipel Myeloma therapy. De IMWG consensus

- **Bortezomib + high dose Dexamethasone +anti-CD38 (Daratumimab)**
- **Lenalinomide is an option in mild and moderate renal insufficiency. Adaptation to the kidney function is required**
- **Thalidomiede should be used with caution.**
- **New:**
  - inhibition of fibril formation (EGCG)
  - SAP depletion (CPHPC)
  - Anti-amyloid antibodies (NEOD001
  - Anti-SAP:
  - Fibril disruption:doxycicline

Renal treatment

- **Plasmapheresis is indicated if hyper viscosity.**
- **Hemodialysis is necessary when CDK 5.**
- **If FLC are involved anti-myeloma therapy will be combined with a Medium cut-off membrane.**
  - Theralite: Eulite study (negative results) Myre-trial (positive results)
  - Theranova (Baxter):cheep and efficiënt

AKI in MM What have we learned?

- The tubulointerstitial injury, cast nephropathy, is the most common cause of severe acute kidney injury in patients with multiple myeloma
- Histology findings of acute tubular necrosis and acute tubulointerstitial nephritis should raise a 'red flag' for potential injury from high levels of free light chains in patients with multiple myeloma
- Standard assessment of renal histology by light microscopy, immunofluorescence and electron microscopy might require the addition of specialist techniques to detect subtle injuries in patients with a monoclonal protein
- Serum immunoassays can provide a rapid alternative to urine electrophoresis for the identification of monoclonal free light chains
- Early diagnosis and intervention remain key to preventing irreversible renal injuries in patients with MM