Multiple Myeloma
Advances for clinical pathologists & histopathologists

CME in Haematology 2014
IAPP & Dept of Pathology, BVDUMC, Pune
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Bombay Hospital Institute of Medical Sciences, Mumbai
Today, we will restrict our talk to myeloma kidney
Present talk is based on our experience of handling 563 patients of multiple myeloma during last 33 years (1981 – 2013), out of whom 128 had initially presented to the nephrologists for renal problem of unexplained origin.
I sincerely thank my nephrology colleagues

- Dr. A.L. Kirpalani
- Dr. Shrirang Bichu
- Dr. Vishwanath Billa
- Dr. Bhupendra Gandhi
- Dr. Hemant Mehta
- Dr. Kirti Upadhyay
- Dr. L.H. Suratkal
- Dr. Arun Shah
- Dr. Bharat Shah
Dr Henry Bence Jones
Saturday, November 1, 1845

Dear Dr Henry Bence Jones,

The tube contains urine of very high specific gravity.

When boiled, it becomes highly opaque.

On the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear.

However, as it cools, assumes the consistence and appearance which you see.

Heat reliquifies it.

What is it?

Drs. Macintyre and Watson
Renal failure in myeloma

• A principal cause of morbidity
• Outcome of myeloma kidney remains poor
• First authentic report was from UK in 1972\(^1\)
• Median survival of myeloma with AKI : 2 months
• Recent data from UK (2010), this has improved to 10 months\(^2\)
• Hence, this remains a great unmet clinical need

1 J Clin Pathol. 1972;25:555-61
2 Nephrol Dial Transplant. 2010;25:419-26
For those who love statistics....
Myeloma & kidney (at presentation)

- 10% have ‘severe’ renal insufficiency requiring dialysis
- 20% have ‘overt’ renal insufficiency but don’t need dialysis
- 50% have ‘renal insufficiency’ if you go by abnormal creatinine clearance
Myeloma and Kidney at presentation

• **70%** of those excreting >10 g/d of light chain develop renal failure

• **90%** of pts requiring dialysis develop ESRD

• **100%** of IgD myeloma develop renal failure
The distribution of monoclonal proteins amongst pts with MM & renal failure
Mechanism of renal failure
Mechanism of renal failure

1. Light chain–dependent
Myeloma kidney is all about FLC & Tamm – Horsfall proteins
Renal failure in myeloma

- FLCs are nephrotoxic
- These are responsible for majority of severe AKI
- Understanding the pathogenesis is a must
- That will identify potential targets for early intervention
- The international kidney & monoclonal gammopathy research group
- Founded in 2010 to enable research in this field
Renal failure in myeloma

- Normally, 500 mg of polyclonal FLCs are produced daily
- These are catabolised by proximal tubule
- Only 1–10 mg appear in urine each day
- In myeloma, their production goes up by hundreds of fold
Mechanism of injury

• These induce:
  • Proximal tubular injury
  • Cast nephropathy (distal tubule)
• Both activate inflammatory cascades leading to tubulo-interstitial fibrosis
• Casts in distal tubule block glomerular flow
• This leads to tubular atrophy & further fibrosis
• Final result: “Light chain Fanconi’s syndrome” & “Cast (Myeloma) kidney”
Light chains filtered

10-30g/day absorption

5-10mg/day in urine

Toxic injury

Distal tubule

Proximal convoluted tubule

Glomerulus

Cortex

Outer medulla

Inner medulla

Cast injury

Thick ascending limb

Light chains + Tamm-Horsfall proteins produce casts
1. Cast nephropathy
“Determinants” of “Cast kidney”

- Ionic composition of the tubule fluid
- Flow rate of tubule fluid
- Concentration of THP (Tamm Horsfall Protein)
- Concentration of FLC
- Factors deciding interaction between THP & FLC
Free light chains

- Risk to kidney is maximum after FLC proteinuria reaches 2 g/day or more
- Not all monoclonal FLCs are nephrotoxic
- There are pts who do not develop AKI despite this
- There are factors intrinsic to FLCs & host
- In addition, there are trigger factors
2. Light chain deposition disease
Light chain deposition disease (LCDD)

- Light chains in LCDD are most often kappa
- Light chains deposit along glomerular and/or tubular ‘basement membrane’
- LCDD causes nephrotic syndrome
LC deposit along glomerular basement membrane
LC deposit along tubular basement membrane
LC deposit along tubular basement membrane
LC deposit along tubular basement membrane
3. AL Amyloidosis
AL amyloidosis

- The light chains involved are usually lambda.
- Congo red stain is positive & there is characteristic apple-green birefringence.
- It leads to proteinuria in nephrotic range.
4. Tubulo–interstitial disease
5. Glomerulonephritis
Glomerulonephritis

- Sanjeev Sethi from MAYO clinic, Rochester
- After auto immune diseases and chronic infections (Hep C), monoclonal gammopathies are the 3rd commonest cause of MPGN
- 28/68 (41%) of pts with MPGN without auto immune diseases and chronic infections had monoclonal gammopathies
Monoclonal gammopathy of undetermined significance
Monoclonal gammopathy of renal significance
## LC–Dependent mechanisms

<table>
<thead>
<tr>
<th>1. Cast nephropathy (Myeloma kidney)</th>
<th>40% of MM with renal dysfunction</th>
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<tbody>
<tr>
<td>2. Light Chain Deposition Disease (LCDD)</td>
<td>Usually kappa light chains Nephrotic–range albuminuria</td>
</tr>
<tr>
<td>3. AL Amyloidosis</td>
<td>Usually lambda light chains Nephrotic–range albuminuria</td>
</tr>
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</table>
## LC–Dependent mechanisms

<table>
<thead>
<tr>
<th>4. Tubulo–interstitial</th>
<th>Most difficult to diagnose</th>
</tr>
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<tbody>
<tr>
<td>5. Glomerulonephritis</td>
<td>Membrenoproliferative (MPGN)</td>
</tr>
<tr>
<td></td>
<td>Diffuse proliferative</td>
</tr>
<tr>
<td></td>
<td>Minimal change</td>
</tr>
<tr>
<td></td>
<td>Membranous</td>
</tr>
<tr>
<td></td>
<td>Crescentic</td>
</tr>
<tr>
<td></td>
<td>Cryoglobulinemic</td>
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Mechanism of renal failure

2. Light chain–independent
## Light chain–Independent mechanisms

<table>
<thead>
<tr>
<th>Volume depletion sepsis</th>
<th>Acute tubular necrosis Precipitates cast nephropathy</th>
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<tbody>
<tr>
<td>Hypercalcemia</td>
<td>Not uncommon</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>Uric acid or phosphate nephropathy</td>
</tr>
<tr>
<td>Medications</td>
<td>Bisphosphonates, NSAID, aminoglycosides, I.V. contrast, loop diuretics, ACE–inhibitors, angiotensin receptor blockers</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Disease, treatment, Ig deficiency</td>
</tr>
<tr>
<td>Plasma cell infiltration (rare)</td>
<td>Advanced or aggressive myeloma</td>
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An important note

- Many pts present with
  - Mild renal impairment
  - Low level of M protein (like MGUS)
  - Mild increase in plasma cells
- Clonality is often difficult to document
- Diagnosis remains uncertain
- Treatment is usually withheld
An important note

Careful follow-up to see rising level of M band together with unexplained or worsening KD warrant early kidney biopsy to document LC deposition as this provides rationale for starting anti-myeloma therapy.
rFLC (κ / λ)

- Normal range : 0.26 – 1.65
- With renal failure : 0.37 – 3.10
- Less or more are diagnostic of clonal disorder
- Ratio remains normal in :
  - Polyclonal hyper-gammaglobulinemia
  - Renal impairment
Protein studies in myeloma

- There is evidence that urine protein studies are no more important
- Katzmann et al studied 1,877 pts of plasma cell dyscrasias
- Diagnostic ability of S. protein electrophoresis + SFLC assay

<table>
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<tr>
<th>Disorder</th>
<th>Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM &amp; WM</td>
<td>100 %</td>
</tr>
<tr>
<td>Smoldering myeloma</td>
<td>99.5 %</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>96.5 %</td>
</tr>
<tr>
<td>LCDD</td>
<td>78 %</td>
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</table>

- **Conclusion**: These 2 tests form a viable alternative to urinary assessment
- SLFC assay & ratio can also be used to assess response to treatment
- A quick response stands for good renal recovery
Kidney biopsy in myeloma

- It should be done early in the course
- It helps in differentiating LC & non-LC mediated renal dysfunction
- Special laboratory techniques needed
Kidney biopsy: Following should be routine

- Light microscopy, immunofluorescence & ultra structure
- Subtle & early renal changes need to be mastered
- Staining for kappa & lambda FLCs
- Careful examination of Ig stains
- In select cases:
  - Ultra structural immuno-labeling
  - Mass spectroscopy
An important note

Any pt with renal damage from LC deposition having clonal plasma cells will be called ‘symptomatic’ myeloma irrespective of the quantity of M band & percentage of plasma cells.
Kidney biopsy & monoclonal FLC

- Renal biopsy: 3% have plasma cell dyscrasia
- It defines the type of renal injury
- It determines the degree of active pathology
- It defines chronicity status
- It predicts prognosis
- It dictates how aggressive the treatment should be
Kidney biopsy: Two poorly identified lesions

- Proximal tubulopathy (acute tubular necrosis)
- An inflammatory tubular interstitial process without casts
- These 2 can be identified but their relationship with FLC remains undefined
Can kidney biopsy tell about reversibility of the lesion?
Pointers to myeloma – 1

- Normal sized kidney
- High S. globulin fraction
- Unexplained hypercalcemia
- Normal complement levels
- Distal renal tubular acidosis
- Fanconi syndrome
Pointers to myeloma – 2

- Urinary sediment is almost always bland (except if there is glomerulonephritis or tubulo–interstitial disease)
- In cast kidney, there is no albuminuria
- Nephrotic range albuminuria occurs with amyloidosis or LCDD – Glomerular type
- Urine dipsticks are insensitive to light chains
New AKI

Exclude myeloma kidney Assessment for FLC clone

FLC clone

Clonal FLC ≥500 mg/l
- Probable FLC tubular interstitial pathology
  - Requires hematology work-up
  - Initiation of disease-specific treatment to reduce serum FLC levels

Clonal FLC <500 mg/l
- Alternative monoclonal FLC pathology
  - Requires renal biopsy
  - Consider hematology work-up

No FLC clone

AKI of another cause

Either

Incidental MGUS
Renal disease + Monoclonal protein

Full assessment of monoclonal protein: serum SPE, IFE and FLC + urine IFE

Evaluation of urinary albumin level

High-level FLC clone + low urinary albumin
- If AKI: probable myeloma kidney
- If CKD: consider Fanconi syndrome, amyloidosis, LCDD
  - Requires hematological work-up
  - Renal biopsy if CKD

High-level FLC clone + high urinary albumin
- Possible LCDD or AL amyloidosis
  - Requires histology assessment (salivary, adipose, kidney)
  - Hematology work-up

Low-level FLC clone + high urinary albumin

Low-level FLC clone + low urinary albumin
- Likely incidental MGUS
Prognosis
Outcome of pts having myeloma kidney

• Their survival is shorter

• Such pts do not tolerate certain treatment modalities

• Reversibility of impaired renal function is an important prognostic factor
Conclusion – 1

• Renal damage is an important complication of myeloma causing morbidity & mortality
• FLCs is the single most important factor in its genesis
• During past 20 years, there is remarkable progress in understanding pathogenesis of AKI
• FLC assay & kidney biopsy are the most important investigations
Conclusion – 2

• A common area of interaction between haematologists and haemato–pathologists
• Both of them need to pick up myeloma as the etiology of renal dysfunction quickly. That can alter the prognosis & save lives
Thank You
Questions