The Kidney in Multiple Myeloma

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Plasma cells produce antibodies that bind to antigens, fighting infection and at times causing disease.
Antibodies
In multiple myeloma, a malignant transformation occurs producing myeloma cell. These cells produce antibodies in excess.
**Multiple Myeloma**

- **Definition:** Malignant proliferation of plasma cells derived from a single clone

- **MM** is a plasma cell dyscrasia that accounts for almost 10% of all hematologic malignancies

- **Etiology:** radiation; mutations in oncogenes; familial causes; role of IL 6

- **Incidence increases with age** Males > females; Blacks > Whites  

*Korbet & Shawartz. JASN September 2006 vol.*
Clinical Manifestations

Bone Pain:
- 70%, precipitated by movement
- Pathological fractures
- Activation of osteoclasts by OAF produced by myeloma cells

Susceptibility to infections:
- Diffuse hypogammaglob. If the M spike is excluded
- Poor antibody responses, neutrophil dysfunction
- Pneumococcus, S. aureus: Pneumonia, pyelonephrits

Clinical Manifestations

Common

- Bone pain and pathological fractures
- Anemia and bone marrow failure
- Infection due to immune-paresis and neutropenia
- Renal impairment

Less common

- Acute hypercalcemia
- Symptomatic hyperviscosity
- Neuropathy
- Amyloidosis
- Coagulopathy
Clinical Manifestations

Renal failure: 25%
- Multiple contributory factors
- Hypercalcemia, hyperuricemia, recurrent infections
- Tubular damage produced by Light chains
- Type 2 proximal RTA, non selective proteinuria

Anemia: 80%
- Normochromic/normocytic
- Myelophthisis: inhibition by cytokines produced by plasma cells.
- Leukopenia/thrombocytopenia only in advanced cases.
**Bone Disease**

- Lytic lesions – 60%

- Osteoporosis, Fx, compression Fx – 20%

- Myeloma cells produce Cytokines that:
  - Stimulate osteoclastic activity
  - Inhibit osteoblastic Activity

70% cellularity, increased atypical plasma cells comprising 60% of cellularity.
Skull infiltrations
Minimal diagnostic criteria for myeloma

- >10% Plasma cells in bone marrow or plasmacytoma on biopsy
- Clinical features of myeloma

- Plus at least one of:
  - Serum M band (IgG > 30 g/l; IgA > 20 g/l)
  - Urine M band (Bence Jones proteinuria)
  - Osteolytic lesions on skeletal survey
Myeloma and The kidney
<table>
<thead>
<tr>
<th>Cause</th>
<th>Manifestation</th>
</tr>
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<tbody>
<tr>
<td>Prerenal</td>
<td></td>
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<tr>
<td>Volume depletion</td>
<td>Hypercalcemia</td>
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<tr>
<td></td>
<td>Gastrointestinal losses (nausea and vomiting)</td>
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<td></td>
<td>Sepsis</td>
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<tr>
<td>Hemodynamic</td>
<td>Hemodynamic from NSAIDs</td>
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<tr>
<td>Other</td>
<td>Hyperviscosity (IgA, IgG₃)</td>
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<tr>
<td></td>
<td>Hyperuricemia</td>
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<td></td>
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<tr>
<td>Renal</td>
<td></td>
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<tr>
<td></td>
<td>Proximal tubular injury from light chains, urate;</td>
</tr>
<tr>
<td></td>
<td>distal tubular injury from casts</td>
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<tr>
<td></td>
<td>Glomerular disease (LCDD, amyloid)</td>
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<tr>
<td>Post Renal</td>
<td></td>
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<td>Calculi</td>
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<td>Colic</td>
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Epidemiology

- Serum creatinine $> 1.5 - 2.0$ mg/dl
- The one-year survival is 80% in pts. with Cr $< 1.5$ compared to 50% in pts. with a Cr $> 2.3$
- Prognosis is especially poor in pts. who require dialysis
Causes of renal failure in MM

- Cast nephropathy
- Light chain deposition disease
- Primary amyloidosis
- Hypercalcemia
- Renal tubular dysfunction
- Volume depletion
- IV contrast dye, nephrotoxic medications
# Renal Pathology in Patients with Multiple Myeloma

<table>
<thead>
<tr>
<th>Histological Finding</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>Myeloma kidney</td>
<td>30%-50%</td>
</tr>
<tr>
<td><em>(Myeloma cast nephropathy)</em></td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis/fibrosis</td>
<td>20%-30%</td>
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<tr>
<td>without cast nephropathy</td>
<td></td>
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<tr>
<td>Amyloidosis</td>
<td>10%</td>
</tr>
<tr>
<td>Light chain deposition disease</td>
<td>5%</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>10%</td>
</tr>
<tr>
<td>Other (urate nephropathy, tubular crystals, hypercalcemia, FSGS)</td>
<td>5%</td>
</tr>
</tbody>
</table>

Myeloma Kidney

Two main pathogenetic mechanisms:
- Intracellular cast formation
- Direct tubular toxicity by light chains

Contributing factors to presence of renal failure due to multiple myeloma:
- High rate of light chain excretion (tumor load)
- Biochemical characteristics of light chain
- Concurrent volume depletion
Cast Nephropathy

- Most common pathological diagnosis on renal biopsy in multiple myeloma
- Due to light chains binding with Tamm-Horsfall mucoprotein, which is secreted by tubular cells in ascending loop of Henle, forming casts
- Multinucleated giant cells surround the casts
- Dehydration worsens cast nephropathy due to decreased flow in tubules, increased concentration of light chains
Cast Nephropathy
Cast Nephropathy
**Light Chain Deposition Disease (LCDD)**

- Most commonly presents with both renal insufficiency and nephrotic syndrome.
- Usually due to kappa (κ) immunoglobulin fragments which deposit in kidneys.
- Circulating light chains are taken up and partially metabolized by macrophages, and then secreted and precipitate, causing tubular injury – and thus, proteinuria.

*Korbet and Schwartz. JASN September 2006 vol. 17 no. 9 2533-2545*
Uptake of light chains by proximal tubular cells. Renal biopsy specimen from a patient excreting κ light chains. Immunoperoxidase staining showing κ light chains along the brush border and in the cytoplasm of the PTC (brown stain).

The tubular basement membranes stained with κ Ig light chain (A) show bright (3+).

Monoclonal Ig deposition disease (MIDD) with diffuse and nodular glomerulosclerosis.

Courtesy of Jean L. Olson, University of California San Francisco
AL-amyloidosis

- AL-amyloidosis is found in up to 30% of patients who present with multiple myeloma; conversely, multiple myeloma is present in up to 20% of patients who present with AL-amyloidosis.

- Proteinuria is the most common renal manifestation at presentation, occurring in up to 80% of patients with the nephrotic syndrome seen in 30 to 50% of these patients.

Amyloidosis

- Usually due to **lambda (λ)** light chains (AL)

- Pathogenesis is similar to LCDD, in that light chains are taken up and partially metabolized by macrophages and then secreted – then precipitate to form fibrils that are Congo red positive, β-pleated

- Like LCDD, due to tubular injury and also presents as nephrotic syndrome

Renal amyloidosis, ultrastructural appearance. Amyloid deposits are seen as randomly arranged, 10-nM fibrils of indefinite length.

Glomerulus stained with Congo red
Hypercalcemia

- Hypercalcemia occurs in multiple myeloma due to bone resorption from lytic lesions

- Serum calcium $> 11.0 \text{ mg/dL}$ occurs in 15% of pts with multiple myeloma

- Hypercalcemia commonly contributes to renal failure by renal vasoconstriction, leading to intratubular calcium deposition
Renal Tubular Dysfunction - Acquired Fanconi syndrome

- On occasion, light chains cause tubular dysfunction without renal insufficiency
- Most commonly occurs with kappa light chains
- Light chains are resistant to protease degradation and have tendency to accumulate in tubule epithelial cells and form crystals
Renal Tubular Dysfunction - Acquired Fanconi syndrome

- Tubular damage due to light chain toxic effects or indirectly from the release of intracellular lysosomal enzymes.

- This presents as Fanconi syndrome - proximal renal tubular acidosis with wasting of potassium, phosphate, uric acid, and bicarbonate.

Renal affection in MM

Two main pathogenetic mechanisms:

- Intracellular cast formation
- Direct tubular toxicity by light chains
Role of IL-6

- IL-6 is an important growth factor for plasma cells in multiple myeloma, and may play a role in myeloma kidney

- IL-6 stimulates acute phase reactants from liver, promoting cast formation and possibly impairing light chain resorption

- IL-6 also contributes to hypercalcemia by stimulating osteoclasts
Hydration with IV fluids

Treatment of hypercalcemia
  ▫ Loop diuretics
  ▫ Caution with bisphosphonates

Treatment of myeloma
  ▫ Pulse steroids +/- thalidomide
  ▫ VAD chemotherapy
  ▫ ASCT

Possible role for plasmapheresis

Dialysis, as necessary
Plasmapheresis in MM

• Theoretical benefit in removing the toxic circulating light chains to spare renal function

• Limited data to support efficacy

• Treatment of choice if hyperviscosity symptoms are present

• Potential risk for bleeding if Dx is needed due to pheresis-induced removal of coagulation factors
**Efficacy of plasmapheresis in multiple myeloma**  
Serum protein electrophoresis before (left panel) and after (right panel) four consecutive daily plasma exchanges in a patient with multiple myeloma and acute renal failure. The monoclonal peak representing the circulating light chains (arrow) has essentially disappeared. Courtesy of Andre Kaplan, MD
FLCs and cast nephropathy
• Plasma exchange is a logical approach, but shows no clinical benefit.

• A 3.5 L plasma exchange removes 65% of intravascular FLCs but has very little impact on overall FLC levels—because they are also present in similar concentrations in the extravascular compartment and tissue edema fluid.

• On the whole, dialyzers are similarly ineffective.
New option for FLC removal

- Until now, there has been little success in attempts to use blood purification
Perhaps....

Renal rescue for myeloma patients
Theralite™ High Cut-off technology

- It is with a new technology for the efficient and direct removal of FLCs.

- High Cut-off technology is uniquely successful in removing FLCs because its large pores do not restrict removal.

**Journal Article**

European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): a randomised control trial.

Colin A Hutchison, Mark Cook, Nils Heyne, Katja Weisel, Lucinda Billingham, Arthur Bradwell, Paul Cockwell

Prevention of renal failure in MM

- IVF hydration
- Discontinuation of nephrotoxic drugs (i.e. NSAIDs, etc.)
- Chemotherapy/steroids – treatment of multiple myeloma to decrease the filtered light chain load
Thank you for your kind attention.