Evaluating Paraproteinemia

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The Paraprotein

- An abnormal immunoglobulin or part of an Ig (light chain) in the blood or urine
- Typically produced by a clonal population of B-cell derived plasma cells
- Elderly > Young
- African Americans > Caucasians
- Common
  - Age > 50 yrs, 3.2% have a paraprotein
  - Age > 70 yrs, 5.3% with paraprotein
- Not always malignancy associated
Paraprotein Structure

**Heavy Chains**
- IgG > IgA
- IgM > IgD

**Light Chains**
- Kappa
- Lambda
Conditions Associated with PP

- **Non-Malignant**
  - Auto-immune d/o’s
    - SLE
    - RA
    - Hashimoto’s thyroiditis
  - **Cutaneous disease**
    - Pyoderma gangrenosum
    - Liver disease
      - Cirrhosis
      - Hepatitis
    - Infectious disease
      - Mycobacterium
      - Bacterial endocarditis

- **Pre-malignant**
  - MGUS

- **Malignant**
  - Solitary Plasmacytoma
  - Myeloma
  - POEMS Syndrome
  - Plasma cell leukemia
  - Amyloidosis
  - Chronic lymphocytic leukemia
  - Waldenstrom Macrogobulinemia
  - Non-Hodgkin Lymphoma
What problems can the protein cause?

- Neuropathy
- Nephropathy (esp. light chains)
- Cytopenias
  - ITP
  - AIHA
- Cold Agglutinins
- Cryoglobulins
When to think about testing for a Paraprotein

- Malaise and fatigue
- Bone disease (persistent pain, osteopenia or lytic lesions)
- Impaired renal function
- Normochromic normocytic anaemia; pancytopenia
- Hypercalcaemia
- Recurrent bacterial infections
- Hyperviscosity
- Nephrotic syndrome, cardiac failure, malabsorption
- Peripheral neuropathies, carpal tunnel syndrome
- Incidental persistent elevated ESR
- Elevated total protein level in serum
Most Commonly Found as a Laboratory Diagnosis

- Typically found when routine testing shows an elevated serum total protein
- Further testing to evaluate PP
  - Serum protein electrophoresis
  - Serum immunofixation electrophoresis
  - Serum free light chain (freelite)
  - Quantitative immunoglobulins
Paraprotein Evaluation

- **SPEP**
  - Quantitative
  - Best test to quantity M protein

- **UPEP**
  - Quantitative
  - Requires 24 hr urine collection

- **Immunoglobulin levels**
  - IgA, IgG, IgM, IgD
  - Abnormal + normal protein

![Serum Protein Electrophoresis Normal](image)

<table>
<thead>
<tr>
<th>Fractions</th>
<th>%</th>
<th>g/dL</th>
<th>Ref. g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>59.7</td>
<td>4.18</td>
<td>3.40 - 5.20</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>2.9</td>
<td>0.20</td>
<td>0.10 - 0.40</td>
</tr>
<tr>
<td>Alpha 2</td>
<td>13.8</td>
<td>0.97</td>
<td>0.50 - 0.90</td>
</tr>
<tr>
<td>Beta</td>
<td>14.2</td>
<td>0.99</td>
<td>0.60 - 1.20</td>
</tr>
<tr>
<td>Gamma</td>
<td>9.4</td>
<td>0.66</td>
<td>0.50 - 1.50</td>
</tr>
</tbody>
</table>

![Serum Protein Electrophoresis Abnormal](image)

<table>
<thead>
<tr>
<th>Fractions</th>
<th>%</th>
<th>g/dL</th>
<th>Ref. g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>36.0L</td>
<td>3.60</td>
<td>3.40 - 5.20</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>1.8</td>
<td>0.18</td>
<td>0.10 - 0.40</td>
</tr>
<tr>
<td>Alpha 2</td>
<td>7.7</td>
<td>0.77</td>
<td>0.50 - 0.90</td>
</tr>
<tr>
<td>Beta</td>
<td>5.5</td>
<td>0.65</td>
<td>0.60 - 1.20</td>
</tr>
<tr>
<td>Gamma</td>
<td>48.0H</td>
<td>4.80</td>
<td>0.50 - 1.50</td>
</tr>
</tbody>
</table>
Paraprotein Evaluation

**IFE**
- Not Quantitative
- Identifies heavy chain (IgG, IgA, IgM) and light chain (λ, κ) protein type
- Most Sensitive test to evaluate for an M-protein
Paraprotein Evaluation- SFLC

- Serum Free Light Chain
  - Assay detects only free LC (cannot bind bound LC)
  - Quantitative
  - Should be correlated to 24 hour urine and UPEP

- Excellent for following disease progression in MGUS, disease response in LC myeloma, and even disease in myeloma after SPEP normal (stringent CR)
- Is used for prognosis in MGUS (later)
Plasma Cell Disorders

- MGUS
- Solitary Plasmacytoma
- Multiple Myeloma
- Waldenstrom Macroglobulinemia
- Amyloidosis
- POEMS Syndrome
- Lymphoplasmacytic lymphoma
Fig 1. Causes of 1684 cases of monoclonal gammopathy diagnosed at Mayo Clinic, 2006. Macro, Waldenström macroglobulinaemia; MGUS, monoclonal gammopathy of undetermined significance; SMM,
Once a PP is found, what further w/u should be performed?

- 70 y/o male with worsening tingling and numbness in a stocking distribution is found to have a serum IgM lambda M-protein of 1.1 gm/dL.

- What further tests should be done?
  
  a. Skeletal survey
  b. Bone marrow biopsy
  c. CT scan of C/A/P
  d. All of the above
  e. b+c only
Once a PP is found what further w/u should be performed?

- Answer
  - b+c only

- Diagnostic tests
  a. CBC diff, plat
  b. Lytes, BUN, Cr, β2m
  c. Serum viscosity
  d. Bone marrow biopsy
  e. CT scan of C/A/P
  f. Anti-MAG antibodies
     (myelin-associated glycoproteins)
  a. Fat Pad biopsy

- Differential Dx IgM
  - WM
  - CLL
  - NHL
  - MGUS
  - Amyloidosis
Further Diagnostic Tests if IgG, IgA or IgD Paraprotein

- If the finding is IgG, IgA, IgD Paraprotein
  - CBC, diff, plat
  - Lytes, Bun, Cr, Ca\(^{2+}\), Albumin, β2 microglobulin
  - Quantitative immunoglobulins: IgG, IgM, IgA
  - Serum light chain, free assay
  - 24 hour urine for total protein, UPEP+IFE
  - Skeletal survey
  - Bone marrow biopsy
  - Fat Pad biopsy
MGUS
# Characteristics of MGUS and Multiple Myeloma

<table>
<thead>
<tr>
<th>Serum Protein Electrophoresis</th>
<th>MGUS</th>
<th>Smoldering Multiple Myeloma</th>
<th>Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb, α₁, α₂, β, γ</td>
<td>![MGUS Peaks]</td>
<td>![Smoldering Multiple Myeloma Peaks]</td>
<td>![Multiple Myeloma Peaks]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone Marrow</th>
<th>&lt;10% Plasma cells</th>
<th>≥10% Plasma cells</th>
<th>≥10% Plasma cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Picture</td>
<td>Asymptomatic</td>
<td>Asymptomatic</td>
<td>Symptomatic</td>
</tr>
<tr>
<td></td>
<td>No end-organ damage</td>
<td>No end-organ damage</td>
<td>End-organ damage present</td>
</tr>
<tr>
<td>Therapy</td>
<td>Observation only</td>
<td>Observation only</td>
<td>Therapy required</td>
</tr>
</tbody>
</table>
MGUS and Outcome


Fig 4. Rate of death from non-plasma cell disorders compared with progression to plasma cell disorders in 1384 patients with monoclonal gammopathy of undetermined significance (MGUS) from southeastern Minnesota.
MGUS

- Usual presentation is asymptomatic elevation of total protein
- Diagnosis of exclusion
  - R/O Myeloma
  - R/O other plasma cell dyscrasias
- No treatment, follow lab tests
- Prognosis
  - Absolute protein level (higher worse)
  - Non-IgG protein (IgG better)
  - Abnormal SFLC ratio
MGUS

- **Prognosis** (Protein >1.5 gm/dL, non IgG, Abnl SFLC)

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>RR</th>
<th>Absolute risk of Progression at 20 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (0 factors)</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>Int Low Risk (1)</td>
<td>5.4</td>
<td>21%</td>
</tr>
<tr>
<td>Int High Risk (2)</td>
<td>10.1</td>
<td>37%</td>
</tr>
<tr>
<td>High Risk (3)</td>
<td>20.8</td>
<td>58%</td>
</tr>
</tbody>
</table>

Monoclonal Gammopathy of Undetermined Significance

Overall 1% progress each yr, correlated with initial paraprotein level, with low risk <1 g/dL, high risk >3 g/dL; \( P<0.001 \)

MYELOMA
Myeloma

- MM is characterized by
  - Increased clonal plasma cells in the bone marrow
  - Overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD, or IgE) or Bence-Jones protein (free antibody light chains) and concomitant drop in other immunoglobulins

Multiple Myeloma: Epidemiology

- Approx 19,000 new cases in US/yr
- Prevalence is 45-50,000 patients
  - Median Age 66 years old
    - Age <50 years: 10%
    - Age <40 years: 2%
  - Increased in African Americans
  - Males >> Females

Presenting Features of MM

CRAB = symptomatic MM

- M-protein SIU: 97%
- Anemia: 73%
- Lytic Bone Lesions: 66%
- Bone Pain: 58%
- Renal Insufficiency: 19%
- Hypercalcemia: 13%
- Minor or no abnormalities: 11%
- Hepatomegaly: 4%
- Amyloidosis: 4%
- Non-secretory (no SIU M-protein): 3%

Adapted with permission from Kyle RA et al. Mayo Clin Proc. 2003;78:21
Myeloma Evaluation

- CBC, Lytes, Cr, Ca\(^2+\), **Albumin**
- Quantitative immunoglobulins, \(\beta_2\) microglobulin
- SPEP, SIFE, SFLC
- 24 hour urine for UPEP, UIFE
- Skeletal survey, **MRI spine**
- BMBx: H+E, Flow, cytogenetics
- Molecular Studies: **FISH, GEP, PCR**
- Optional: **PET**, bone density exam, CRP
- Future: **markers for apoptosis**
Bortezomib +/- Dex: Confirmation of Remission: PET Scan

Plasmacytomas

Jagannath et al. ASH 2004; Abstract 333
International Staging System (ISS)

- **Stage I**
  - B2M < 3.5 mg/L
  - Albumin >/= 3.5
  - OS 62m

- **Stage II**
  - B2M < 3.5
  - Albumin <3.5 g/dL
  - or
  - B2M >/= 3.5 – 5.5
  - OS 45m

- **Stage III**
  - B2M > 5.5
  - OS 29m

### Graphs

**A**
- Months From Initial Chemotherapy Treatment
- Percentage
- Median in months
- Stage I: 655/1,196, 62 (58, 67)
- Stage II: 1,029/1,551, 45 (42, 47)
- Stage III: 1,050/1,388, 29 (26, 31)

**B**
- Months From Initial Chemotherapy Treatment
- Percentage
- Median in months
- Stage I: 606/1,111, 62 (58, 65)
- Stage II: 1,054/1,606, 44 (42, 48)
- Stage III: 968/1,305, 29 (26, 32)
Beyond ISS: Cytogenetics and FISH

- **Good risk**
  - normal cytogenetics
  - hyperdiploidy
  - t(11;14)

- **Poor risk**
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - del 17p (by FISH)
  - del 13 (by metaphase cytogenetics)
  - hypodiploidy (by metaphase cytogenetics)
  - LDH > 2 x uln
Survival slide
U.S. Multiple Myeloma: Treatment Outline

1. Adapted from International Myeloma Foundation; 2001. Reprinted with permission

Asymptomatic

Active Myeloma

Therapy

Relapse

Plateau Remission

Symptomatic

Refactory Relapse

MGUS* or Smoldering Myeloma

Therapy

Therapy

Therapy

~15,000 New cases in U.S.²

~45,000 Annual patients in the U.S.³

11,000 deaths/yr. in U.S.²

M Protein (g/l)

~20

0

~100

20

50

100

~15,000 New cases in U.S.²

~45,000 Annual patients in the U.S.³

11,000 deaths/yr. in U.S.²

* MGUS: Monoclonal Gammopathy of Undetermined Significance
Myeloma Treatment

- Acute Management
- Supportive Care
- Primary Anti-Myeloma therapy
  - Radiation
  - Chemotherapy
  - Biologic therapy
  - Autologous Transplantation
- Long-Term Therapy
  - Maintenance therapy
- Cure??
  - Allogeneic Transplantation
  - Combinations of new drugs + autologous transplant
Pathophysiology

MM Cells in Bone Marrow Microenvironment

- MM cells
- Bone Marrow Vessels
- VEGF, bFGF
- ICAM-1
- Bone Marrow Stromal Cells
- IL-6↑
- TNFα↑
- IL-1β↑
- PBMC
- CD8+ T Cells
- NK Cells
- IL-2↑
- IFNγ↑

Reprinted with permission from Richardson PG et al. Blood. 2002;100:3063
Myeloma Treatment

- Acute Management
  - Infections: humoral and cell-mediated deficits
    - Antibiotics/Antivirals
      - Encapsulated organisms (pneumococcus)
      - Viral infections (zoster)
      - Pneumocystis Carini
    - Vaccines (esp. pneumococcal, varicella)
  - Pain Medications
  - Hypercalcemia (bisphosphonates)
  - Renal Insufficiency (HD, plasma exchange (?))
  - Cord compression (Surgery, XRT, steroids)
Multiple Myeloma – Supportive Care

- **Bone Directed Therapy**
  - Vit D/ Ca2+
  - Avoid Steroids (?)
  - Bisphosphonates
    - Zoledronic acid
    - Pamidronate
    - Universally given
    - Best for those with BD
    - ? some anti-MM effects
  - Side Effects
    - Renal insufficiency
    - Osteonecrosis of Jaw
      - Avoid surgery
      - Antibiotics
      - Limit duration of BP

- **Neuropathy**
  - 30% have PN at diagnosis
  - Sensory>motor
  - Many MM drugs cause PN
  - Preventatives
    - Alpha-lipoic acid
    - L-carnitine
    - Vit B6
  - Treat Pain
    - Gabapentin
    - Duloxetine (Cymbalta)
    - Amitriptyline (Elavil)
    - Pregabalin (Lyrica)
    - Narcotics

- **Bone Directed Therapy**
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  - Avoid Steroids (?)
  - Bisphosphonates
    - Zoledronic acid
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    - Universally given
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    - Narcotics
## Multiple Myeloma Treatment 1990’s
### Response Rate and Median Survival

<table>
<thead>
<tr>
<th>Initial Treatment</th>
<th>% Response</th>
<th>Median Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>VAD</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>M2 Protocol</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Interferon</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>NO CR’s</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Initial Therapy for Myeloma: 2000’s +

- Rapidly Evolving
  - 5 Active treatments
    - Thalidomide
    - Lenalidomide
    - Bortezomib
    - Pegylated Liposomal Doxorubicin (PLD)
    - Autologous Stem Cell Transplant
  - Many New Agents
    - Carfilzomib
    - Pomalidomide
  - Combinations
Two Important Classes of Drugs for MM

- **IMID: Immune modulatory drugs**
  - MOA remains to be fully characterized
    - Pro-apoptotic properties
    - Anti-angiogenic properties
    - Inhibits the secretion of pro-inflammatory cytokines
  - Thalidomide, Lenalidomide, Pomalidomide

- **Proteasome Inhibitors**
  - MOA remains to be fully elucidated
    - Reversible inhibitor of the proteasome
    - Inhibits NFκ-B
    - Pro-Apoptotic
    - Affects unfolded protein response
  - Bortezomib, Carfilzomib
Lenalidomide: Treatment Responses

- **Relapse and Refractory**
  - CR ~5%
  - PR ~30-40%

- **Upfront/First-line therapy**
  - Best when combined with steroids (Dexamethasone)
    - CR 20-30%
    - PR ~90%
  - In combination with Biaxin + Dexamethasone
    - CR 40%
    - PR 95%
  - Dexamethasone 40 mg given once weekly (pulse dexamethasone (4 days in a row) increases toxicity)
  - Must anticoagulate
Bortezomib and Proteasome Inhibition\textsuperscript{1-3}

**26S Proteasome**

- Degrades ubiquitinated proteins
- Proteolysis is adenosine triphosphate (ATP) dependent

Bortezomib: Treatment Responses

- **Relapse and Refractory**
  - CR ~9%
  - PR ~30-40%

- **Upfront/First-line therapy**
  - Best when combined with steroids (Dexamethasone)
    - CR 10-20%
    - PR ~90%
  - In combination with Doxil +/- Dexamethasone
    - CR 35-40%
    - PR >90%
  - In combination with Thalidomide/Revlimid +/- Dex
    - CR 30-40%
    - PR 100%
## Multiple Myeloma Treatment 2000’s

### Response Rate and Median Survival

<table>
<thead>
<tr>
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<th>%CR</th>
<th>Median Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPT</td>
<td>&gt;90%</td>
<td>~7-20%</td>
<td>45m</td>
</tr>
<tr>
<td>Bort/Dex</td>
<td>85-90</td>
<td>~10%</td>
<td>?</td>
</tr>
<tr>
<td>Len/Dex</td>
<td>&gt;90%</td>
<td>~20%</td>
<td>?</td>
</tr>
<tr>
<td>Thal/Bort/Dex</td>
<td>&gt;90%</td>
<td>~30%</td>
<td>?</td>
</tr>
<tr>
<td>PAD</td>
<td>&gt;90%</td>
<td>~25%</td>
<td>?</td>
</tr>
<tr>
<td>VDD</td>
<td>&gt;90%</td>
<td>~25%</td>
<td>?</td>
</tr>
<tr>
<td>RVD</td>
<td>&gt;95%</td>
<td>~20-25%</td>
<td>?</td>
</tr>
</tbody>
</table>
Myeloma Survival by Decade

Improved due to new drugs:

- Thalidomide
- Lenalidomide
- Bortezomib
THANK YOU