An Approach to the Patient with Monoclonal Gammopathy

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Overview

• Define “monoclonal gammopathy”
• How do patients with monoclonal gammopathy present?
• Care of the patient with monoclonal gammopathy
Monoclonal gammopathy

- The presence of an excessive amount of an immunoglobulin in serum
  - IgG
  - IgA
  - IgM

Monoclonal gammopathy

Normal SPEP  Abnormal SPEP
Monoclonal gammopathy

• Depending on the nature of the monoclonal gammopathy, patients may present with a wide range of conditions:
  – Asymptomatic, incidentally discovered
  – Critically ill with multi-organ system dysfunction

Patient 1

• A 68 year old man presents for routine blood work. He has hyperlipidemia and receives regular blood work to monitor liver function tests related to his statin medication.
  – He has no complaints and feels well.
  – His examination is without abnormal findings.
Patient 1

• A 68 year old man presents for routine blood work. He has hyperlipidemia and receives regular blood work to monitor liver function tests related to his statin medication.
  – His LFTs show normal AST and ALT.
  – Total protein is 8.8 g/dL (normal 6.4-8.3 g/dL)
  – Albumin is 3.7 g/dL (normal 3.4-4.8 g/dL)

Patient 1

• The patient has an unexplained, widened “protein gap”
  – Total protein is 8.8 g/dL (normal 6.4-8.3 g/dL)
  – Albumin is 3.7 g/dL (normal 3.4-4.8 g/dL)

• **PEARL:** albumin typically accounts for about half of total protein in serum
Patient 1

- To investigate the elevated total protein:
  - SPEP
  - Quantitative immunoglobulin levels
  - Monoclonal immunofixation

- SPEP: “A prominent zone of restriction in the gamma region, suggestive of monoclonal gammopathy”

Patient 1

- Quantitative immunoglobulins:
  - IgG (600-1500mg/dL) 1920 mg/dL
  - IgA (100-400mg/dL) 220 mg/dL
  - IgM (50-300mg/dL) 240 mg/dL

- Monoclonal immunofixation:
  - IgG kappa monoclonal protein 1145 mg/dL
Patient 1

- Further blood work is performed:
  - Normal blood counts
  - Normal metabolic panel and kidney function
  - Normal blood calcium level

Patient 1

- The patient is referred to a hematologist for input
  - A bone marrow biopsy is normal except for 4% monoclonal plasma cells.
  - A radiograph skeletal survey is normal.

- The patient is given a diagnosis of “monoclonal gammopathy of uncertain significance”
Monoclonal gammopathy of uncertain significance (MGUS)

- Definition of MGUS:
  - Monoclonal protein < 3 g/dL
  - Bone marrow plasma cells < 10%
  - Absence of signs or symptoms

MGUS epidemiology

- Prevalence:
  - 3.2% of Caucasians > 50 years old
  - 5.3% in patients > 70 years old
  - More common in men than women
  - Prevalence is twice as high in African-Americans
  - 2-3 fold increase in first degree relative of patient
  - Average age at diagnosis is 70 years

- Cause is unknown
  - Higher prevalence in obesity, chronic antigen stimulation, pesticide exposure
### MGUS management

- **MGUS**
  - No treatment required
  - Patients must be followed, however, because of risk of progression to clinical malignancy:
    - Multiple myeloma
    - Amyloidosis
    - Waldenstrom’s macroglobulinemia
    - Non-Hodgkin lymphoma

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### MGUS management

- The overall risk of MGUS progressing to clinical malignancy is 1% per year
  - The actual observed rate is a bit lower because patients are far more likely to die of an unrelated condition in long term follow up
  - However, patients with MGUS require lifelong follow up as progression has been reported up to 30 years after index presentation
MGUS management

• There is no way to tell if an individual with MGUS will progress or not, however:
  – Monoclonal protein > 2g/dL = 40% lifetime risk
  – IgA or IgM has 2-fold increase risk than IgG

Patient 1

• Conclusion:
  – The patient has been observed on a 6-month basis without evidence of disease progression.
  – At two years follow up, he will begin annual re-evaluation of his MGUS
MGUS key points

- Almost always an incidental finding
  - Remember to check the protein gap on LFTs!
- No treatment indicated
- Most patients will not progress to malignancy
  - However, virtually all patients require life long follow up

Patient 2

- A 58 year old woman presents for her annual examination. She feels well.
  - Her past medical history includes hypertension for which she takes atenolol.
  - Her examination is without abnormalities
Patient 2

• A 58 year old woman presents for her annual examination. She feels well.

  – She recently attended a “health fair” at her employer’s request and presents results of blood work obtained at the event.

Patient 2

• On review, her blood counts are normal.
• Her comprehensive metabolic panel is entirely normal except for:

  – Total protein is 9.0 g/dL (normal 6.4-8.3 g/dL)
  – Albumin is 3.9 g/dL (normal 3.4-4.8 g/dL)
Patient 2

- This asymptomatic patient also has an unexplained protein gap.

- Her SPEP reveals: “a marked zone of restriction in the gamma region compatible with a paraprotein:

  Patient 2

  - Quantitative immunoglobulins:
    - IgG (600-1500mg/dL) 650 mg/dL
    - IgA (100-400mg/dL) 2930 mg/dL
    - IgM (50-300mg/dL) 52 mg/dL

  - Monoclonal immunofixation:
    - IgA kappa monoclonal protein 2745 mg/dL
### Patient 2

- She sees a hematologist:
  - A bone marrow biopsy which shows 23% monoclonal plasma cells
  - A radiographic skeletal survey shows no lytic lesions

- She is diagnosed with “smoldering myeloma”

### Smoldering myeloma

- **Definition:**
  - Monoclonal IgG or IgA protein > 3 g/dL
  - or
  - >10% clonal plasma cells in bone marrow

- Absence of clinical signs or symptoms
Smoldering myeloma

- Smoldering myeloma:
  - Accounts for about 8% of all cases of multiple myeloma
  - Median age 64
  - More common in men than women
  - Often an incidental diagnosis

Smoldering myeloma management

- No treatment required*
  - Clinical trials are currently evaluating early intervention
- Patients are typically assessed every 3-4 months for signs or symptoms of progression
- Most commonly patients progress to multiple myeloma or amyloidosis
## Risk of progression

### Table: Risk of Progression

<table>
<thead>
<tr>
<th>Variable:</th>
<th>progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal protein:</strong></td>
<td></td>
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<tr>
<td>&gt; 4 g/dL</td>
<td>80  80  90</td>
</tr>
<tr>
<td>&lt; 4 g/dL</td>
<td>47  64  71</td>
</tr>
<tr>
<td>IgA</td>
<td>66  77</td>
</tr>
<tr>
<td>IgG</td>
<td>46  62</td>
</tr>
<tr>
<td><strong>Bone marrow plasma cells (%)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>36  53</td>
</tr>
<tr>
<td>20-50</td>
<td>68  82  92</td>
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<tr>
<td>&gt; 50</td>
<td>85  93</td>
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</tbody>
</table>
Smoldering myeloma management

• Patients are typically assessed every 3-4 months for signs or symptoms of progression

• In this case, Patient 2 has been followed for nearly 30 months now without evidence of progression.
  – She is considering participation in an early intervention clinical trial at present

Smoldering myeloma key points

• No treatment required
  – Consider referral for clinical trial participation

• Risk of progression:
  – much higher for SM than MGUS
  – Risk of progression is highest in first 5 years
  – IgA, high monoclonal protein or high bone marrow plasma cells increase risk of progression
### Patient 3

- A 62 year old man is brought into the clinic by his daughter.
  - She says over the past two days he has become increasingly confused and disoriented.
  - He was seen about 3 months ago for back pain that seemed to improve with a short course of non-steroidal anti-inflammatory medication

<table>
<thead>
<tr>
<th>Temperature 100.2</th>
<th>HR 115</th>
<th>RR 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pale, disoriented to place and time</td>
<td></td>
<td></td>
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<tr>
<td>Mucous membranes very dry</td>
<td></td>
<td></td>
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<tr>
<td>Tachycardic, regular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen is tender to palpation</td>
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Patient 3

<table>
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<tr>
<th>A 62 year old man is brought into the clinic by his daughter.</th>
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<tbody>
<tr>
<td>- Basic laboratory results show:</td>
</tr>
<tr>
<td>- WBC 14 K/uL (normal 4-10 K/uL)</td>
</tr>
<tr>
<td>- Hemoglobin 8.2 g/ dL (normal 13-17 g/dL)</td>
</tr>
<tr>
<td>- Platelets 122 K/uL (normal 150-400 K/uL)</td>
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<td></td>
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</tbody>
</table>

Patient 3

<table>
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<tr>
<th>A 62 year old man is brought into the clinic by his daughter.</th>
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<tbody>
<tr>
<td>- Basic laboratory results show:</td>
</tr>
<tr>
<td>- Total protein is 10.2 g/dL (normal 6.4-8.3 g/dL)</td>
</tr>
<tr>
<td>- Albumin is 3.2 g/dL (normal 3.4-4.8 g/dL)</td>
</tr>
<tr>
<td>- BUN 44 mg/dL (normal 6-20mg/dL)</td>
</tr>
<tr>
<td>- Creatinine 2.4 mg/dL (normal 0.8-1.2mg/dL)</td>
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<tr>
<td>- Calcium 13.8 mg/dL (normal 8-10 mg/dL)</td>
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</tbody>
</table>
• The patient is transferred to a local emergency room and admitted to hospital
  
  − Hypercalcemia is treated with IV fluids
  
  − He is seen by a consultant from hematology

• Quantitative immunoglobulins:
  
  − IgG (600-1500mg/dL) 4225 mg/dL
  − IgA (100-400mg/dL) 50 mg/dL
  − IgM (50-300mg/dL) 35 mg/dL

• Monoclonal immunofixation:
  
  − IgG kappa monoclonal protein 3928 mg/dL
Patient 3

• A bone marrow biopsy reveals 64% monoclonal plasma cells

• A radiographic skeletal survey shows numerous lytic lesions with compression fractures in the lumbar spine

• The patient is diagnosed with multiple myeloma

Multiple myeloma

• A monoclonal protein
• Clonal plasma cells in bone marrow
• Signs and symptoms of disease:
  – Calcium elevation
  – Renal insufficiency
  – Anemia
  – Bone disease
    • Also: hyperviscosity, recurrent infections
Multiple myeloma

- 20,000 new cases annually in USA
- About 75,000 patients living with MM
- About 12,000 deaths annually

- Incurable
- Prevalence of disease is rising
- Cause is essentially unknown

Multiple myeloma

- NEW information!
  - Multiple myeloma is universally preceded by MGUS
  - New treatments have improved survival
    - 6 new FDA approved therapies in last 6 years
    - Median survival doubled in last 10 years
  - Treatment paradigms rapidly changing
    - Consider referral to multiple myeloma center
Patient 3

- The patient received aggressive in-hospital care
  - His serum creatinine normalized
  - He was started on induction treatment and achieved remission
  - He underwent high-dose chemotherapy with autologous bone marrow transplantation
  - He is alive and well in remission 4 years out from index presentation

Multiple myeloma key point

- Index of suspicion:
  - Early presentation with non-specific signs and symptoms
    - Back pain (lytic bone disease)
    - Mental status changes (hypercalcemia)
    - Fatigue (anemia)
    - Recurrent / unusual infections
    - Pain in extremities (hyperviscosity)

    - Renal insufficiency (hypertension / diabetes)
Monoclonal gammopathy

- MGUS
- Smoldering myeloma
- Multiple myeloma

- Also seen in:
  - Amyloidosis (usually just in urine)
  - Waldenstrom’s macroglobulinemia (IgM)
  - Chronic lymphocytic leukemia and non-Hodgkin lymphoma

More information

- [http://cancer.osu.edu](http://cancer.osu.edu)
  - KEYWORD SEARCH: Myeloma

- MGUS
  - JAMA 2010;vol304:2397-404
- Smoldering myeloma
  - J Clin Oncol 2010;vol 28: p 690-7
- Multiple myeloma
  - New Eng J Med 2011;vol 364: p 1046-60