Hematology: Understanding the Immunoglobulins and Bone Marrow Diseases

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Disclosures

• Presenter: Dr. Andrea Lee

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  • Consulting Fees: None
  • Other: None

• Potential for conflict(s) of interest: None
Objectives

- Know the indications for ordering a serum protein electrophoresis (SPEP)
- Learn to interpret the SPEP
  - Understanding polyclonal versus monoclonal gammopathy
- Develop an approach to investigating a monoclonal protein (MCP)
- Be aware of the diseases associated with MCPs
- Know when to refer to hematology
Case 1

- 60 F postmenopausal
- Hx of hypertension, dyslipidemia, DM2
- BMD shows osteoporosis - no back pain or fractures
- Basic investigations
  - Complete blood count (CBC) – normal
  - Creatinine, Ca\(^{2+}\), Phos, Mg\(^{2+}\) normal
  - Liver function tests normal, TSH normal
  - 25(OH)D low, PTH normal
- Your colleague suggests order a SPEP but you’re not sure it is required....
Interactive Question

- In the work-up of post-menopausal osteoporosis, a serum protein electrophoresis is....

A. Always indicated  
B. Sometimes indicated in selected patients  
C. Never Indicated
In the work-up of post-menopausal osteoporosis, a serum protein electrophoresis is….

A. Always indicated
B. Sometimes indicated in selected patients
C. Never Indicated
Primary Care Testing for SPEP

- No indication for routine testing on PHE
- Common indications:\n  - Suspected immunodeficiency
  - Chronic inflammatory conditions (RA, SLE) or chronic infections (e.g., hepatitis C, HIV).

Primary Care Testing for SPEP

- Symptoms suspicious for multiple myeloma, Waldenström’s macroglobulinemia, amyloidosis
  - New-onset anemia + renal failure + bone pain
  - Rouleaux formation on peripheral blood smear
  - Back pain
  - Unexplained pathologic fracture or lytic lesion
  - Hypercalcemia
  - Renal insufficiency
  - Proteinuria
  - Unexplained peripheral neuropathy
  - Osteoporosis work up in selected patients
SPEP in Osteoporosis

- Prevalence of secondary osteoporosis is unknown
  - 26 – 27% of women and men > age 50 yr
  - as high as 60% in one study on men alone \(^2,3\)

- SPEP recommended in SELECTED patients
  - Canadian: vertebral or atypical fractures \(^4\)
  - National Osteoporosis Foundation - SPEP, SFLCR and IFE \(^5\)
  - North American Menopause Society 2010 \(^6\)
  - Am Assoc of Clinical Endocrinologists – SPEP, SFLCR \(^7\)
  - Endocrine society (men) \(^8\)
SPEP in Osteoporosis

- “Selected” subject to interpretation
- Fractures, osteopenia, osteoporosis age <65 years
- Symptom directed testing
- Fracture history

- Monoclonal protein found in 2.1% of patients screened\(^1\)

Case 1: Now what?

- You order a SPEP and find a monoclonal protein of 2 g/L

- What should you do?
  A. Refer to hematology
  B. Forget about the result, it isn’t significant
  C. Repeat testing in 6 months
  D. Order more tests to see if this is something significant
  E. Both C and D
Case 1: Now what?

- You order a SPEP and find a monoclonal protein of 2 g/L

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Understanding the SPEP

- Proteins migrate in the electrical field according to charge, size, and shape
- Densitometric scan of the gel separation

# Interpreting the SPEP

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Dehydration</td>
<td>Protein loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Protein-losing enteropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hemorrhage, burns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver disease</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>Estrogen effect (Pregnancy)</td>
<td>Alpha1-antitrypsin deficiency</td>
</tr>
<tr>
<td></td>
<td>Acute phase reactant: infection, injury, trauma</td>
<td></td>
</tr>
<tr>
<td>Alpha 2</td>
<td>Acute / chronic inflammation</td>
<td>Malnutrition, Megaloblastic anemia, Protein-losing enteropathies</td>
</tr>
<tr>
<td></td>
<td>Estrogen effect</td>
<td>Hemolysis, liver disease</td>
</tr>
<tr>
<td></td>
<td>nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>steroid use, hyperthyroidism</td>
<td></td>
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## Interpreting the SPEP

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<tr>
<td>Beta</td>
<td>Hyperlipidemia, iron-deficiency anemia</td>
<td>Protein malnutrition</td>
</tr>
<tr>
<td>Gamma</td>
<td>Polyclonal gammopathy</td>
<td>Agammaglobulinemia Hypogammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>• Chronic infections</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Malignancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cirrhosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• CTD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monoclonal gammopathy (IFE)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MGUS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Multiple Myeloma, amyloidosis, Waldenstrom’s Macroglobulinemia</td>
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Abnormal SPEP: Monoclonal Protein

- Single class of immunoglobulins secreted by abnormally expanded plasma cell clone
- Uses:
  - Screens and quantifies MCP
- Limitations:
  - Insensitive to small MCP
  - Does not subtype MCP (e.g. IgG λ etc)

AKA: M-protein, M-spike, paraprotein

**Additional Tests**

- **Quantitative immunoglobulins**
  - ↓ in immunodeficiency
  - ↑ in polyclonal vs monoclonal gammopathy

- **Immunofixation**
  - Typing of MCP
  - Differentiates between monoclonal vs polyclonal gammopathy
  - Doesn’t quantify protein → must order SPEP

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*SPEP and IFE alone will miss ~15% of plasma cell dyscrasias* ¹

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Additional Testing

- 24 hour urine for Urine PEP and immunofixation
  - Bence Jones protein = monoclonal protein or light chain found in the urine
- Limitations\textsuperscript{12}:
  - Not sensitive to small M-proteins
  - Cumbersome to perform
  - Difficult to interpret with concentrated samples or heavy proteinuria containing polyclonal proteins
- Combined serum and urine PEP and IFE studies 97% sensitivity for plasma cell dyscrasia\textsuperscript{13}

Serum Free Light Chains (SFLC)

- Normal kappa : lambda RATIO is 2:1
  - Highly abnormal RATIOS $\rightarrow$ monoclonal gammopathy
  - Borderline abnormal ratio $\rightarrow$ interpret with caution, can be due to polyclonal gammopathy and renal impairment

- Uses:
  - Dx of non or oligo secretory MM, amyloidosis
  - Predicting progression for MGUS, smoldering MM, plasmacytoma
  - Monitoring residual disease

Serum Free Light Chains (SFLC)

- Limitations:
  - imprecision, especially with different lots of FLC reagent $^{14}$

- Sensitivity of SPEP + IFE + SFLCR approximately 97.4% for all PCD$^{13}$

- international guidelines recommend that SFLC testing replace urine electrophoresis in the diagnosis of monoclonal gammopathies

Imaging

- **Skeletal survey:**
  - Detects lytic bone lesions, osteopenia, fractures
  - Not routinely indicated if other investigations suggest MGUS
  - Nuclear bone scan not useful - lack of osteoblastic activity (i.e. can be normal)

- **CT abdo/pelvis**
  - To detect lymphadenopathy in patients in whom Waldenstrom’s is highly suspected or confirmed.
How to Investigate a MCP

MCP on SPEP → IFE

IgG, IgA, IgD kappa or lambda
CBC, Cr, Ca2+, alb, SFLCR, urine studies

IgG MCP <15 g/L
Normal SFLCR
No CRAB

Yes
Low Risk MGUS

Normal Skeletal Survey and No CRAB

Bone marrow *

MGUS

No
Skeletal Survey

Abnormal Skeletal Survey or CRAB

Multiple Myeloma

Other s/s: Cardiac, GI, Renal, Neuro, Skin

ECHO
Fat pad biopsy +/- organ biopsy
If positive

AL Amyloidosis

See next slide

IgM kappa or lambda

See next slide
How to Investigate a MCP

IgM kappa or lambda

CBC, Cr, Ca2+, alb, SFLCR, urine studies
Skeletal Survey, CT Abdo / Pelvis
Bone Marrow **

Normal XR
No CRAB
Normal CT

Abnormal Skeletal Survey or CRAB

≥10% Plasma Cells
IgM MCP >30 g/L

No

MGUS

Yes

Smoldering Waldenstrom’s

IgM Multiple Myeloma

Other s/s:
Cardiac, GI, Renal, Neuro, Skin

Lymphadenopathy, Splenomegaly
Cytopenias

Waldenstrom’s

ECHO
Fat pad biopsy +/− organ biopsy

If positive

AL Amyloidosis
“CRAB” Symptoms

- C = Hypercalcemia: Ca^{2+} > 2.8 mmol/L
- R = Renal failure: Cr > 177 or GFR < 40 ml/min
- A = Anemia: Hb < 100 or > 20 g below baseline
- B = Bony lesions (lytic lesions, plasmacytoma)
# Case 1

## Lab results

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<th>Results</th>
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What is the most likely diagnosis?

1. Monoclonal protein of Undetermined Significance (MGUS)
2. Multiple myeloma
3. Amyloidosis
4. Waldenstrom’s Macroglobulinemia
5. I have no idea
## Case 1

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What is the most likely diagnosis?

1. MGUS
2. Multiple myeloma
3. Amyloidosis
4. Waldenstrom’s Macroglobulinemia
5. I have no idea
DDx Monoclonal Gammopathies

- Plasma Cell Disorders
  - Solitary plasmacytoma
  - Multiple myeloma
  - POEMS

- Lymphocytic Disorders
  - Waldenstrom’s Macroglobulinemia
  - Heavy-Chain Diseases

- Infiltrative and Deposition Diseases
  - AL amyloidosis
  - Immunoglobulin Deposition Disease

- Miscellaneous
  - MGUS
  - Transplant related Monoclonal Gammopathy
DDx Monoclonal Gammopathies

Monoclonal Gammopathies

n=39,929

- Lymphoproliferative 3% (1,298)
- Amyloidosis 9.5% (3,781)
- Multiple myeloma 17.5% (6,974)
- MGUS 58% (23,179)
- SMM 4% (1,494)
- Solitary or extramedullary 2% (774)
- Macro 2% (940)
- Other 4% (1,489)

Mayo Clinic 1960-2008

## Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MGUS</strong></td>
<td>MCP &lt;30g/L</td>
<td><strong>SMM</strong> MCP (IgG or IgA) ≥30g/L <strong>OR</strong></td>
<td>Clonal BMPC ≥10% with any level M-protein <strong>OR</strong></td>
</tr>
<tr>
<td></td>
<td>AND Clonal BMPC &lt;10%</td>
<td><strong>URINARY</strong> MCP ≥500mg/24h</td>
<td>Plasmacytoma</td>
</tr>
<tr>
<td></td>
<td>AND No “CRAB” or amyloidosis or end-organ damage</td>
<td><strong>AND/OR</strong> Clonal BMPC 10-60% <strong>AND</strong></td>
<td><strong>AND “CRAB”</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No “CRAB” or amyloidosis</td>
<td><strong>OR Any 1 of</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• &gt; 60% clonal plasma cells on bone marrow</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Serum iFLC/uFLC &gt;100 (level iFLC is at least 100mg/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• &gt;1 focal lesion on MRI at least 5mm in size.</td>
</tr>
</tbody>
</table>

MGUS

- **Prevalence**
  - 1.3% of healthy blood donors, 3% of adults >50 years old, 8% of adults >85 years old.\textsuperscript{18,19}
  - 2-3 x more common in African Americans \textsuperscript{20}

- **Disease associations** \textsuperscript{21}
  - Plasma cell disorders, amyloidosis, LPD
  - CIDP
  - Kidney/liver transplant

MGUS

- Disease associations \(^{21}\)
  - Osteoporosis and increased risk of fractures
    - Increased pro-osteoclast and anti-osteoblast cytokines
  - Possible compromised bone microarchitecture and strength \(^{22}\)
  - Level of the paraprotein in the blood does not seem to correlate with this increased risk \(^{3}\)

- Possible associations:
  - Chronic infection, CTD, Thrombophlebitis

Risk of Progression MGUS

All 3 factors abnormal 2.9%/yr
Any 2 factors abnormal 1.9%/yr
Any factor abnormal 1%/yr
Serum M-spike <1.5g/dL, IgG subtype + normal SFLCR 0.25%/yr

Risk Factors:
- MCP >15 g/L
- Non IgG MCP
- Abn SFLCR

## MGUS – IMWG Guidelines

<table>
<thead>
<tr>
<th>MGUS Risk Category</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low – 0 risk factors</td>
<td>▪ Baseline BM or skeletal survey not routinely indicated if other investigations suggest MGUS</td>
</tr>
<tr>
<td></td>
<td>▪ Repeat SPEP in 6 months</td>
</tr>
<tr>
<td></td>
<td>▪ If stable, repeat every 2–3 years or when symptoms of arise</td>
</tr>
<tr>
<td>Intermediate - High</td>
<td>▪ Baseline bone marrow *</td>
</tr>
<tr>
<td></td>
<td>▪ CT abdomen if IgM MCP</td>
</tr>
<tr>
<td></td>
<td>▪ If still MGUS, repeat CBC/SPEP in 6 months then yearly for life</td>
</tr>
<tr>
<td></td>
<td>▪ Reassess earlier if symptoms arise</td>
</tr>
</tbody>
</table>

MGUS: Other considerations

- Consider DXA to assess BMD given association with osteopenia/osteoporosis 24
- Optimize Vitamin D and calcium doses
- If osteoporosis or osteopenia identified → consider therapy with bisphosphonates 25,26
- If fractures develop 24
  - Refer to bone specialist
  - Consider kyphoplasty for treating symptomatic vertebral compression fractures

Case 1:

- You monitor the patient over 3 years and repeat BW shows …

<table>
<thead>
<tr>
<th>Measure</th>
<th>2013</th>
<th>2016</th>
</tr>
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<tbody>
<tr>
<td>Hb/ WBC/Plt</td>
<td>125/5.0/300</td>
<td>100/3.5/250</td>
</tr>
<tr>
<td>Creatinine</td>
<td>79</td>
<td>185</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.30</td>
<td>2.42</td>
</tr>
<tr>
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<td>40</td>
<td>40</td>
</tr>
<tr>
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<td>SFLCR (range 0.26 – 1.65)</td>
<td>1.48</td>
<td>13.69</td>
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Case 1:

- What should you do?
  A. Repeat skeletal survey and if normal, re-evaluate in 12 months
  B. Repeat skeletal survey and if normal, re-evaluate in 6 months
  C. Repeat skeletal survey and if normal, re-evaluate in 3 months
  D. Refer to hematology
Case 1:

- What should you do?
  A. Repeat skeletal survey and if normal, re-evaluate in 12 months
  B. Repeat skeletal survey and if normal, re-evaluate in 6 months
  C. Repeat skeletal survey and if normal, re-evaluate in 3 months
  D. Refer to hematology
When to refer to:

**IgG, IgA, IgD kappa or lambda**

- **IgG MCP <15 g/L**
  - Normal SFLCR
  - No CRAB
  - **Low Risk MGUS**
    - Repeat CBC, Cr, Ca2+, SPEP, urine studies in 6 months
    - If stable, follow-up q 2-3 years

- **IgG MCP >15 g/L**
  - IgA or IgD MCP
  - Abnormal SFLCR
  - No CRAB
  - **URGENT Heme Referral**

- **CRAB or other symptoms**
  - Routine referral to Heme

**IgM kappa or lambda**

- **No CRAB or other symptoms**
  - Routine referral to Heme

- **CRAB or LN, HSM, Cardiac, GI, Renal, Neuro, Skin**
  - URGENT referral to Heme
Case 1: Multiple Myeloma

Lytic Lesions on X-Ray

Bone Marrow Biopsy


28. Maslak, Peter. ASH Image Bank
AL Amyloidosis

Symptoms:

- Cardiac: Arrhythmias, CHF, orthostatic hypotension, syncope
- Renal: Proteinuria, edema, renal failure
- GI: Nausea, diarrhea, constipation, loss of appetite, weight loss
- Other: bruising, skin lesions
- Neuro: Neuropathy

Periorbital Bruising

Macroglossia


30. Pocket Dentistry. [http://pocketdentistry.com/diseases-of-the-tongue/#Fig1](http://pocketdentistry.com/diseases-of-the-tongue/#Fig1).
Take Home Points

- SPEP should be used in primary care to investigate:
  - Patients with symptoms suggestive of plasma cell disorders
  - Selected patients with osteoporosis

- SPEP and immunofixation help to differentiate between polyclonal versus monoclonal gammopathy

- Look for “CRAB” symptoms to differentiate between MGUS and more serious diseases
Take Home Points

- Low risk MGUS can be followed by primary care physicians

- Refer to hematology when:
  - MCP >15 g/L
  - Non IgG MCP
  - Abnormal light chain ratio
  - CRAB symptoms, cardiac, neurologic, GI, LN, HSM, skin or constitutional s/s
References


References


References


References


29. Silverstein, Sophie R MB. Primary, systemic amyloidosis and the dermatologist: Where classic skin lesions may provide the clue for early diagnosis. Dermatology Online Journal. 2005; 11(1).