When do I order an SPEP and how do I interpret the results?

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Disclosures

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Objectives

1. List the indications for ordering a serum protein electrophoresis (SPEP)

2. Understand the difference between a polyclonal and monoclonal gammopathy

3. Develop a logical approach to the investigation of an M-protein
# Referral to Hematology

Dear Dr. [Name]

Please see [lab results] for persistent abnormalities to SPEP, see attached.

<table>
<thead>
<tr>
<th>Protein Electroph-Serum</th>
<th>Flags</th>
<th>Results</th>
<th>Reference Range</th>
<th>Units</th>
</tr>
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<tbody>
<tr>
<td>Total Protein (serum)</td>
<td>N</td>
<td>73</td>
<td>60 - 80</td>
<td>g/L</td>
</tr>
</tbody>
</table>

**Protein Electroph-Serum**
- Alb SerPl Elph-mCnc
- A1 Globulin SerPl Elph-mCnc
- A2 Globulin SerPl Elph-mCnc
- B-Globulin SerPl Elph-mCnc
- G-Globulin SerPl Elph-mCnc
- 093-5 GDML

**Protein Electroph-Urine**
- Polyclonal gammopathy.
- No light chains noted
Interactive question

1. What do you do next?

   a. Investigate for multiple myeloma with CBC, creatinine, calcium, skeletal survey
   b. Repeat test in 6 months
   c. Investigate for reactive causes including liver disease, connective tissue diseases, infection
   d. Order CT chest/abdo/pelvis
Dear Cancer Care Manitoba - Intake - McCharles Unit,

I am writing to request you assessment of this patient regarding what I believe to be [Redacted] presented near the end of July, with lower back pain which had been getting worse over a two month period. He has enjoyed very good health in the past. His only medical problem has been hypertension which has been well controlled with a combination of Ramipril 10mg daily and Hydrochlorothiazide 12.5mg daily. I did not find any dramatic findings on his physical examination. An xray of his lumbar spine revealed compression fractures in his lower thoracic and lumbar spine. A CT scan has also been performed and I shall enclose a copy of that report. His recent blood work has shown mild anemia, mild impairment of his renal function and elevated calcium as well as an M band on his protein electrophoresis at 1.8g/L. I do not yet have the results of his urine protein electrophoresis but will forward that result when it is available. I am also obtaining a MRI of his spine and a skeletal survey and will forward those results when available.

Thank you for seeing this patient.
Interactive question

1. What is the most likely diagnosis?

   a. MGUS
   b. Multiple myeloma
   c. Diffuse large B cell lymphoma
   d. Waldenstrom’s macroglobulinemia
   e. Chronic myeloid leukemia
When to ORDER SPEG and how to INTERPRET RESULTS

WHEN TO ORDER AN SPEG:
- Unexplained anemia, back pain
- Osteopenia, osteolytic lesions, spontaneous fractures
- Renal insufficiency with bland urinary sediment
- Heavy proteinuria or Bence Jones proteinuria
- Hypercalcemia with normal PTH
- Hypergammaglobulinemia
- Immunoglobulin deficiency
- Unexplained peripheral neuropathy
- Recurrent infections
- Elevated ESR or serum viscosity
- Peripheral blood smear showing rouleaus

If clinical suspicion remains high for plasma cell disorder and SPEG is negative ➔ obtain serum free light chain ratio (SFLCR)

CRAB SYMPTOMS**:
- C = Ca2+ > 2.8
- R = creatinine > 177 umol/L or GFR < 40 mL per min
- A = hemoglobin < 100 g/L or 20 g/L below normal
- B = lytic lesions

**Attributable to plasma cell disorder

OTHER SPEG RESULTS

POLYCLONAL GAMMOPATHY (reactive)
- Investigate for other causes including:
  - Liver disease
  - Connective tissue disease
  - Infection

OLIGOCLONAL GAMMOPATHY (usually reactive)
- Repeat test in 6–12 months if clinically indicated (see top box “When to order an SPEG”)

ELEVATED FREE LIGHT CHAINS - NORMAL RATIO (reactive)
- Investigate for other causes including:
  - Kidney disease
  - Liver disease
  - Connective tissue disease
  - Infection

Monoclonal (M) protein identified

Subtype igG, igA, igD
- Kappa or Lambda

Steps:
1. M-protein concentration
2. CBC, creatinine, Ca2+ (to evaluate CRAB symptoms)
3. Serum free light chain ratio (SFLCR)
4. UA to assess proteinuria

IgG M-protein < 15 g/L
- Normal SFLCR
- No CRAB

Low Risk Monoclonal Gammopathy of Undetermined Significance (MGUS)

Repeat SPEG in 6 months; if stable then q1-2 years or with CRAB symptoms

Order Skeletal Survey

Skeletal survey ABNORMAL OR CRAB symptoms
- Suspect Multiple Myeloma (MM)

Skeletal survey NORMAL AND no other CRAB symptoms
- Suspect MGUS or Smoldering Multiple Myeloma (SMM)

URGENT Referral to CCMB Hematology

Referral to CCMB Hematology

Suspect Waldenstrom’s Macroglobulinemia

Suspect Lymphoma DSG

CT chest / abdomen / pelvis to assess for lymphadenopathy

AND Steps:
1. M-protein concentration
2. CBC, creatinine, Ca2+ (to evaluate CRAB symptoms)
3. Serum free light chain ratio (SFLCR)
4. UA to assess proteinuria

If any of the following present:
- lymphadenopathy OR
- splenomegaly OR
- anemia (hgb < 105 g/L)
Serum Protein Electrophoresis (SPEP)

- Serum protein migrate into bands based on their size and charge
- Limitations:
  - Not sensitive when M-protein is small
  - Cannot classify type of M-protein
Serum immunofixation

- Used to determine clonality
  - Monoclonal versus polyclonal
- Not able to quantitate the concentration of the M band
- Must be done in conjunction with the SPEP
  - Does not give the concentration of the M-protein
Definition of Monoclonal Protein

- Monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells in an amount that can be detected by immunofixation of serum and/or urine/other fluids

- Also known as: M-protein, paraprotein, M-spike, M-component, M-band
<table>
<thead>
<tr>
<th>Type of M-protein</th>
<th>Associated plasma cell disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact immunoglobulin (heavy &amp; light chain)</td>
<td>Myeloma</td>
</tr>
<tr>
<td></td>
<td>Other lymphoproliferative disorders – Waldenstrom macroglobulinemia</td>
</tr>
<tr>
<td>Light chain only</td>
<td>Light chain myeloma</td>
</tr>
<tr>
<td></td>
<td>Light chain deposition disease (usually kappa)</td>
</tr>
<tr>
<td></td>
<td>AL amyloidosis (usually lambda)</td>
</tr>
<tr>
<td>Heavy chain only</td>
<td>Heavy chain disease (alpha, gamma, mu)</td>
</tr>
<tr>
<td></td>
<td>Heavy chain deposition disease</td>
</tr>
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</table>
When to order an SPEP?

**DIAGNOSIS**

- Unexplained anemia, back pain
- Osteopenia, osteolytic lesions, spontaneous fractures
- Renal insufficiency with bland urinary sediment
- Heavy proteinuria or Bence Jones proteinuria
- Hypercalcemia with normal PTH
- Hypergammaglobulinemia
- Immunoglobulin deficiency
- Unexplained peripheral neuropathy
- Recurrent infections
- Elevated ESR or serum viscosity
- Peripheral blood smear shows rouleaux

***If clinical suspicion remains high and SPEP is negative, then order a serum free light chain ratio (SFLCR)***
When to ORDER SPEP and how to INTERPRET RESULTS

**WHEN TO ORDER AN SPEP:**
- Unexplained anemia, back pain
- Osteopenia, osteolytic lesions, spontaneous fractures
- Renal insufficiency with bland urinary sediment
- Heavy proteinuria or Bence Jones proteinuria
- Hypercalcemia with normal PTH
- Hypergammaglobulinemia
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If clinical suspicion remains high for plasma cell disorder and SPEP is negative ➔ obtain serum free light chain ratio (SFLCR)

**CRAB SYMPTOMS**:
- C – Ca2+ >2.8
- R – creatinine >177 umol/L or GFR <40mL per min
- A – hemoglobin <100g/L or 20g/L below normal
- B – lytic lesions

**OTHER SPEP RESULTS**

**POLYCLONAL GAMMOPATHY** (reactive)
- Investigate for other causes including:
  - Liver disease
  - Connective tissue disease
  - Infection

**OLIGOCLONAL GAMMOPATHY** (usually reactive)
- Repeat test in 6 – 12 months if clinically indicated (see top box “When to order an SPEP”)

**ELEVATED FREE LIGHT CHAINS - NORMAL RATIO** (reactive)
- Investigate for other causes including:
  - Kidney disease
  - Liver disease
  - Connective tissue disease
  - Infection

**Monoclonal (M) protein identified**

**Subtype IgG, IgA, IgD**
- Kappa or Lambda

**Steps**:
1. M-protein concentration
2. CBC, creatinine, Ca2+ (to evaluate CRAB symptoms)
3. Serum free light chain ratio (SFLCR)
4. U/A to assess proteinuria

**IgG M-protein <15g/L**

**Low Risk Monoclonal Gammopathy of Undetermined Significance (MGUS)**
- Repeat SPEP in 6 months, if stable then q1-2 years or with CRAB symptoms

**Order Skeletal Survey**

**Suspect Multiple Myeloma (MM)**

**Suspect MGUS or Smoldering Multiple Myeloma (SMM)**

**URGENT Referral to CCMB Hematology**

**Routine Referral to CCMB Hematology**

**Suspect Waldenstrom’s Macroglobulinemia**

**CT chest / abdomen / pelvis to assess for lymphadenopathy**

**AND Steps**:
1. M-protein concentration
2. CBC, creatinine, Ca2+ (to evaluate CRAB symptoms)
3. Serum free light chain ratio (SFLCR)
4. U/A to assess proteinuria

If any of the following present:
- lymphadenopathy OR
- splenomegaly OR
- anemia (hgb <105g/L)

**Referral to CCMB Lymphoma DSG**

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.
SPEP – interpretation

- Normal
  - No M protein present

RESULTS
SERUM MONOCLONAL PROTEIN INVESTIGATION
Serum Total Protein 61
Serum Albumin 34
No M protein present.
SPEP – interpretation

- Polyclonal gammopathy

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<td>Alb Serpi Elph-mCnc</td>
<td>N</td>
<td>73</td>
<td>60 - 80</td>
<td>g/L</td>
</tr>
<tr>
<td>A1 Globulin Serpi Elph-mCnc</td>
<td>N</td>
<td>42.8</td>
<td>38 - 54</td>
<td>g/L</td>
</tr>
<tr>
<td>A2 Globulin Serpi Elph-mCnc</td>
<td>N</td>
<td>1.3</td>
<td>1 - 3</td>
<td>g/L</td>
</tr>
<tr>
<td>B-Globulin Serpi Elph-mCnc</td>
<td>N</td>
<td>6.7</td>
<td>5 - 9</td>
<td>g/L</td>
</tr>
<tr>
<td>G-Globulin Serpi Elph-mCnc</td>
<td>N</td>
<td>8.9</td>
<td>6 - 11</td>
<td>g/L</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>13.3</td>
<td>5 - 12</td>
<td>g/L</td>
</tr>
</tbody>
</table>

Polyclonal gammopathy.
No light chains noted

Normal

Polyclonal pattern
SPEP - Interpretation

- Monoclonal gammopathy
SPEP - Interpretation

- Monoclonal gammopathy

**SERUM MONOCLONAL PROTEIN INVESTIGATION**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Total Protein</td>
<td>78</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>37</td>
</tr>
<tr>
<td>IgG</td>
<td>16.40*</td>
</tr>
<tr>
<td>IgA</td>
<td>0.36*</td>
</tr>
<tr>
<td>IgM</td>
<td>0.22*</td>
</tr>
</tbody>
</table>

Monoclonal Immunoglobulin: PRESENT

Class/type: Previous IgG / Kappa

Monoclonal Ig concentration: 14

**NOTE:** IgG, IgA and IgM results include normal and concentration when present.

Serum Electrophoresis
Beyond the SPEP

• If only SPEP is done – about 15% of myeloma / other disorders WILL BE MISSED because SPEP will be negative

• What can be done about this?
  – Urine Protein ElectroPhoresis (UPEP)
  – Serum free light chain ratio (SFLCR)
Serum free light chain index/ratio (SFLCI/R)

- **Diagnosis**
  - Non-secretory, oligosecretory, light chain myeloma, and amyloidosis

- **Prediction of risk of progression for MGUS, smoldering myeloma, and plasmacytoma**

- **More sensitive than SPEP for monitoring for residual disease**
Investigating an M-Protein

M-protein detected

Subtype IgG, IgA, IgD kappa or lambda

Subtype IgM: CT chest/abd to look for adenopathy plus step #1-3

STEPS:
1. M-protein concentration
2. Skeletal survey, CBC, creatinine, calcium, β2 microglobulin, albumin (to evaluate CRAB symptoms)
3. Free light chain index (FLCI)

Monoclonal gammopathy of unknown significance (MGUS)
1. M-protein <30 g/L or <10% plasma cells in bone marrow
2. No “CRAB”
3. FLCI can be used for prognosis

Smoldering multiple myeloma (SMM)
1. M-protein >30 g/L or >10% plasma cells in bone marrow
2. No “CRAB”
3. FLCI can be used for prognosis
4. FLCI can be used to follow malignant clone

Symptomatic multiple myeloma (MM)
1. Bone marrow plasmacytosis >10% AND
2. Any “CRAB” attributable to M-protein
3. FLCI can be used to follow malignant clone
<table>
<thead>
<tr>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>M protein in serum &lt;30g/l <strong>and</strong></td>
<td>M protein &gt;30g/l <strong>and</strong>/ <strong>or</strong></td>
<td>Any level of M protein (none in non-secretory) <strong>and</strong></td>
</tr>
<tr>
<td>Clonal BMPC &lt;10% and low level of infiltration on trephine <strong>and</strong></td>
<td>Clonal BMPC &gt;10% <strong>and</strong></td>
<td>Clonal BMPC &gt;10% <strong>and</strong></td>
</tr>
<tr>
<td>No myeloma related “CRAB”</td>
<td>No myeloma related “CRAB”</td>
<td>Myeloma related “CRAB”</td>
</tr>
<tr>
<td>No evidence of other B cell LPD or light chain associated Amyloidosis or other tissue damage</td>
<td></td>
<td>Or : BM plasma cells &gt;60% FLCR &gt;100 &gt;1 focal lesion on MRI</td>
</tr>
</tbody>
</table>

Rajkumar et al. 2014 Lancet Oncology; 15:e538-48
Myeloma related “CRAB”

• C = hypercalcemia (Ca >2.8mmol/L)
• R = renal failure (Cr >177) or GFR <40ml/min
• A = anemia (Hb<100 or > 20g below baseline)
• B = bony lesions (lytic lesions, plasmacytoma)
  ****Attributable to the plasma cell disorder

• New criteria 2014: bone marrow plasma cells >60%; involved/uninvolved SRLFR >100; >1 focal lesion on MRI

Rajkumar et al. 2014 Lancet Oncology; 15:e538-48
Monoclonal Gammopathy

N = 46,739

MGUS
57% (26,552)

Multiple Myeloma
18% (8,336)

AL amyloidosis
9.5% (4,490)

Lymphoproliferative
3% (1,410)

SMM
4% (1,780)

Solitary or extramedullary plasmacytoma
2% (899)

Macro
2.5% (1,236)

Other
4% (2,036)

Mayo Clinic 1960-2002
MGUS is common

Figure 1. Prevalence of MGUS According to Age.
The bars represent 95 percent confidence intervals. Years of age greater than 90 have been collapsed to 90 years of age.

Kyle et al, NEJM 2006;354:1362-9
MGUS

3 adverse risk factors:
1. M band >15g/L
2. Non-IgG subtype
3. Abnormal FLC ratio

Rajkumar et al, Blood 2005;106:812-7
Smoldering myeloma

3 risk factors:
1. M band >30g/L
2. Bone marrow plasmacytosis >10%
3. FLC ratio 0.125 or >8

Figure 1  Risk stratification for smoldering multiple myeloma. The
When to ORDER SPEP and how to INTERPRET RESULTS

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If clinical suspicion remains high for plasma cell disorder and SPEP is negative ➔ obtain serum free light chain ratio (SFLCR)

OTHER SPEP RESULTS

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**Attributable to plasma cell disorder

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Steps:
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CT chest / abdomen / pelvis to assess for lymphadenopathy AND Steps:
1. M-protein concentration
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IgG M-protein <15 g/L
Normal SFLCR
No CRAB

Low Risk Monoclonal Gammopathy of Undetermined Significance (MGUS)

Repeat SPEP in 6 months, if stable then q1-2 years or with CRAB symptoms

Order Skeletal Survey

Suspect Multiple Myeloma (MM)

Suspect MGUS or Smoldering Multiple Myeloma (SMM)

URGENT Referral to CCMB Hematology

Referral to CCMB Hematology

Suspect Waldenstroms Macroglobulinemia

Fe.8, 2015: ©Hematology DSG FINAL (Rimmer)
Take Home Messages

• Monoclonal proteins are common
• Order an SPEP when clinically suspicious of the disorders associated with an M band
• If SPEP negative and still suspicious, then order SFLCR
• When M band identified, investigate for CRAB symptoms
When to refer to hematology

- High suspicion of multiple myeloma (CRAB or lytic lesions)
- MGUS / smoldering myeloma that is not low risk
- Include with referral: CBC, lytes, urea, creatinine, Ca2+, albumin, SPEP and FLC results, skeletal survey
- If skeletal survey not complete – please order
Questions?

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