Elevated Immunoglobulins and Paraproteins

NWL Pathology GP Study Afternoon
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Learning objectives

- Recognise the main abnormalities of serum immunoglobulins
- Differentiate neoplastic from non-neoplastic immunoglobulin disorders
- Use a practical diagnostic algorithm to diagnose the underlying disorder
- Understand the diagnostic and prognostic value of paraprotein
- How to use paraproteins for monitoring and clinical management
B cell development and disease

Bone marrow
- Common Lymphoid Progenitor
- Pro-B cell
- Pre-B cell
- Immature B cell
- Mature B cell

Lymphoid organs
- Marginal zone
  - plasmablast
  - Short-lived plasma cell

Germinal center
- Somatic Hypermutation (SHM)
- Class Switch Recombination (CSR)
- centroblast
- centrocyte
- apoptosis

Myeloma
- IgG or IgA
- Long-lived plasma cell

Waldenstrom’s - Lymphoma
- IgM

Blood
- plasmablast
- memory B-cell
Immunoglobulin structure

Light chain: Kappa or Lambda

Heavy chain: IgM, IgD or IgG, IgA, IgE

Boyd & Joshi, Microbiology Spectrum 2014
Laboratory methods to detect abnormal immunoglobulins

- Serum protein electrophoresis
Laboratory methods to detect abnormal immunoglobulins

Immunofixation

normal

IgGkappa PP

IgGlambda PP

IgGkappa PP
Laboratory methods to detect abnormal immunoglobulins
Serum free light chains
Abnormal immunoglobulins

- Elevated polyclonal immunoglobulins
- Monoclonal immunoglobulin (paraprotein)
- Hypoglobulinaemia
A practical approach to abnormal immunoglobulins

1. Are immunoglobulin levels decreased?

Hypoglobulinaemia (low immunoglobulin levels)

- Hereditary conditions
  - family history, recurrent infections, IgA deficiency
- Acquired
  - Nephrotic syndrome
  - immunosuppressive therapies
  - chronic lymphocytic leukaemia (CLL)
  - light chain or non-secretory myeloma: check serum free light chains
A practical approach to abnormal immunoglobulins

2. Are elevated immunoglobulin levels polyclonal or monoclonal?

Polyclonal immunoglobulins*

- Chronic infection (osteomyelitis, endocarditis, HIV, EBV)
- Inflammation, IgG4 related disease
- Autoimmune (RA, SLE, Sjogren)
- Neoplasm (lung, liver, gastric, rare T cell lymphomas)
- Liver disease (cirrhosis, chronic hepatitis)

* May include several tiny monoclonal bands
A practical approach to abnormal immunoglobulins

3. Presence of monoclonal immunoglobulin: IgM or non-IgM

IgM paraproteinaemia
- IgM MGUS
- Waldenstrom’s macroglobulinaemia / lymphoplasmacytic lymphoma
- Marginal zone lymphoma
- Other non-Hodgkin lymphoma

IgG or IgA paraproteinaemia
- MGUS
- Myeloma (smouldering and symptomatic)
- Plasmacytoma
- Amyloidosis
- POEMS
IgM paraproteins*

Clinical evaluation for Waldenstrom’s other B cell NHL

- Anaemia
- Lymphadenopathy
- Splenomegaly
- Hyperviscosity (more common than in other PP)
- B symptoms
- Neuropathy, even in otherwise asymptomatic patients
- Proteinuria
- NO bone lesions

Infiltration of the bone marrow by lymphoplasmacytic lymphoma sets the diagnosis of Waldenstrom’s macroglobulinaemia

- IgM MGUS has higher risk for progression than IgG MGUS

*It is not synonymous to M-spike
IgM paraproteins

When to refer to haematology

- IgM PP >10g/L or
- Any size IgM PP and symptoms

Patients with symptoms from a known underlying condition (e.g., Rheumatoid arthritis) and a small IgM PP may not require referral.

Asymptomatic individuals with a small IgM PP <10g/L, if not referred to haematology they will require monitoring by their GP every 3-4 months initially, if stable every 6-12 months.

*Increase of an IgM PP >25% (minimum 5g/L) may indicate progression and should trigger referral.*
IgA and IgG paraproteins and/or elevated serum FLC

<table>
<thead>
<tr>
<th>MGUS</th>
<th>smouldering myeloma</th>
<th>symptomatic myeloma</th>
<th>remitting relapsing</th>
<th>refractory plasma cell leukaemia</th>
</tr>
</thead>
</table>
| <10% PC<br>PP <30g/L<br>no organ damage or symptoms | ≥10% PC<br>+/-<br>PP ≥30g/L<br>no organ damage or symptoms | ≥10% PC or plasmacytoma<br>Any PP in serum and/or urine<br>organ damage & symptoms | circulating PC<br>extramedullary disease<br>Death | Amyloidosis, POEMS
IgG / IgA paraproteins and/or elevated serum FLC

Clinical evaluation for MGUS or myeloma (any size PP)

- Anaemia (Hb <100g/L or drop by 20g/L from baseline)
  - >70% of patients at presentation, normocytic

- Bone disease (80%)
  - Bone pain, lytic lesions, osteopenia, fractures

- Hypercalcaemia

- Renal impairment (20 - 40%)
  - Cast nephropathy, always check FLC not only PP

- Infections
  - Bacterial & viral
IgG / IgA paraproteins and/or elevated serum FLC

Imaging for MGUS or myeloma

• Skeletal survey XR films: obsolete

• Whole body low-dose CT scan
• CT PET scan
• Whole-body diffusion-weighted MRI
IgG / IgA paraproteins and/or elevated serum FLC

Clinical evaluation for possible amyloidosis (any size PP)

• Macroglossia
• Unexplained heart failure
• Peripheral neuropathy
• Postural hypotension
• Carpal tunnel syndrome
• Erectile dysfunction
• Proteinuria – nephrotic syndrome

Tip: Always check a urine sample for proteinuria
IgG, IgA and light chain MGUS
(monoclonal gammopathy of undetermined significance)

The most common pre-malignant condition: 3.5% of individuals aged >50 years

Regression or progression

Risk for progression: 1% annually
- IgG and IgA → myeloma
- Light chain → light chain myeloma or renal disease
MGUS risk stratification

Mayo Clinic criteria

<table>
<thead>
<tr>
<th>Risk group</th>
<th>No. of patients</th>
<th>Relative risk</th>
<th>Absolute risk of progression at 20 y (%)</th>
<th>Absolute risk of progression at 20 y, accounting for death as a competing risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (serum M protein, &lt;1.5 g/dL; IgG subtype, normal; free light chain ratio, 0.26-1.65)</td>
<td>449</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low-intermediate-risk</td>
<td>420</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Any 1 factor abnormal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-intermediate-risk</td>
<td>226</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>Any 2 factors abnormal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>53</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
</tr>
<tr>
<td>All 3 factors abnormal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Blood, the American Society of Hematology.

- **Tip**: normal range serum free light chains ratio is higher in renal failure
MGUS risk stratification

The association of PP level and progression risk

Table VIII. Association between the level of M-protein and risk of progression at 20 years.

<table>
<thead>
<tr>
<th>M-protein level (g/l)</th>
<th>Risk of progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>14</td>
</tr>
<tr>
<td>&lt;10</td>
<td>16</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25</td>
</tr>
<tr>
<td>&lt;20</td>
<td>41</td>
</tr>
<tr>
<td>&lt;25</td>
<td>49</td>
</tr>
<tr>
<td>&lt;30</td>
<td>64</td>
</tr>
</tbody>
</table>

Gregersen et al, 2001a; Van De Donk et al, 2001; Rosiñol et al, 2007).
# MGUS risk stratification

**Spanish Group criteria**

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Risk of progression at 7 years</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2%</td>
<td>49%</td>
</tr>
<tr>
<td>1</td>
<td>16%</td>
<td>45%</td>
</tr>
<tr>
<td>2</td>
<td>72%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Perez-Persona et al. (n=311)*

- >95% aberrant bone marrow plasma cells
- Evolving MGUS

**Evolving MGUS**: >10% PP increase in 6 months of progressive increase

**Flow cytometry for normal and malignant plasma cells**
**MGUS management**

**Recommendations for referral to Haematology**

BCSH guidelines, British Journal Haematology 2009

- IgA PP $>$10g/L or IgG PP $>$15g/L
- Bence Jones proteinuria $>$500mg/L
- Any size PP and symptoms

**Recommendations from the International Myeloma Working Group**

Leukemia 2010

- Cases should be risk stratified
- Adjust follow up to risk
- Low risk MGUS can be followed less frequently, every 2-3 years or if they develop symptoms
MGUS-related conditions
Monoclonal gammopathy of renal significance (MGRS)

• Rare condition
• No symptoms or criteria of myeloma / lymphoma
• The physicochemical properties of the Ig and not the amount are important

Early treatment of the myeloma clone is required
Smouldering myeloma

Definition of smouldering multiple myeloma
Both criteria must be met:
• Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
• Absence of myeloma defining events or amyloidosis

Lancet Oncol 2014; 15: e538–48

• Mayo Clinic Risk Stratification:
  • Bone marrow plasma cells ≥10%
  • PP ≥30g/L
  • FLC ratio <0.125 or >8

Tip:
FLC ratio >100 is a diagnostic criterion for myeloma

• Low, intermediate risk: observation
• High risk (3 factors): ?treatment
Serum PP and FLC in myeloma to measure response

<table>
<thead>
<tr>
<th>Standard IMWG response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stringent complete response</strong></td>
</tr>
<tr>
<td><strong>Complete response</strong></td>
</tr>
<tr>
<td><strong>Very good partial response</strong></td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
</tr>
<tr>
<td><strong>Minimal response</strong></td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
</tr>
</tbody>
</table>

- Modern therapies offer high rates of complete response and stringent complete response
- Deeper response → longer remission
- The aim of myeloma treatment should be stringent complete response with negative minimal residual disease in the bone marrow
Serum PP and FLC to diagnose myeloma progression

The prevalence of myeloma in the community increases with aging population and novel effective therapies leading to longer survival

Criteria for progressive myeloma

Any one or more of the following criteria:

- Increase of 25% from lowest confirmed response value in one or more of the following criteria:
  - Serum M-protein (absolute increase must be ≥0.5 g/dL);
  - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL;
  - Urine M-protein (absolute increase must be ≥200 mg/24 h);
- In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL);
- In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%);
- Appearance of a new lesion(s), ≥50% increase from nadir in SPDS$ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis;
- ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease

- PP increase >25% from nadir (minimum 5g/L) defines progressive disease

- In light chain myeloma: > difference FLC by 25% (minimum >10mg/L)
Suggested algorithm for investigation of new PP

**NEWLY FOUND M-PROTEIN IN SERUM**

IgG, IgA, IgD or IgE M-protein

- Assess patient for symptoms or signs of myeloma and AL amyloidosis
- Consider performing X-rays of symptomatic areas
- Exclude anaemia, hypercalcaemia, renal impairment

  **REQUEST IMMUNOFIXATION TO ELUCIDATE IMMUNOGLOBULIN HEAVY AND LIGHT CHAIN ISOTYPE**
  - Ensure level of serum M-protein is quantified
  - Send spot urine for detection of BJP
  - Request serum immunoglobulin levels

**LOW RISK GROUP**

- IgG M protein < 15 g/l
- IgA M protein < 10 g/l
- Asymptomatic
- No other abnormal results
- BJP positive or negative
- Uninvolved immunoglobulins low or normal

Follow up by non-haematologist:

- Repeat serum or urine electrophoresis every 3–4 months and extend interval to 6–12 months if stable and no symptoms
- Supply patient with information leaflet

**HIGH RISK GROUP**

- Symptomatic of suspected myeloma or lymphoproliferative disorder
- Abnormal physical signs suggestive of underlying plasma cell or lymphoproliferative disorder
- Unexplained abnormal investigation results (blood or X-ray)
- IgG M-protein > 15 g/l
- IgA M-protein > 10 g/l
- Any IgD or IgE M-protein irrespective of concentration

Clinical concern during follow up:

Refer to Haematologist for investigation and management

BCSH guidelines,
British Journal Haematology 2009
SUMMARY

- Increased polyclonal immunoglobulins rarely due to haematological disease
- Serum free light chain assay has changed the field, use together with protein electrophoresis and immunofixation
- IgM PP (MGUS, lymphoma) vs non-IgM PP (MGUS, myeloma)
- Clinical evaluation is of paramount importance
- Link symptoms with the presence of PP: myeloma & lymphoma but also amyloidosis, MGRS, neuropathy
- Risk stratification driven clinical management