IgA Smoldering Myeloma

Kelly Paulson, MD, PhD
Discussant: Dr. Thomas Chauncey
Hematology Fellows Conference
30th June 2017
Clinical case

- 65 y/o M, iron deficiency anemia (mild, Hgb > 10) -> SPEP
  - + non-quantifiable IgA spike
- Workup:
  - Hgb 11
  - LFCL 171, ratio lambda/kappa 11
  - UPEP w/immunofix negative
  - Bone marrow bx with 10% clonal plasma cells
  - Skeletal survey by XR negative
Does our patient have....

- MGUS
- Smoldering myeloma
- Myeloma
- Needs more information...
Plasma cell disorders - IMWG

- MGUS
  - Non-IgM MGUS***
  - IgM MGUS
  - Light chain MGUS
- Plasmacytoma
  - Solitary
  - With minimal marrow involvement
- POEMS
- Systemic AL Amyloidosis

- WM
- Smoldering myeloma***
- Multiple Myeloma***

Rajukmar et al, Lancet Oncol 2014
Distribution of Monoclonal Gammopathies

MGUS > 50% of all MG

N = 46,739
Mayo Clinic Database, 1960–2012
Incidence may differ with other populations


Slide: Dr. Chauncey
Work-up of suspected myeloma (IMWG)

• H&P
• Bloodwork: CBC/d, smear, chem, ca+, SPEP w/immunofix
• Urine: 24H for protein, UPEP, immunofix, albuminuria
• BM aspirate and biopsy -> cyto, FISH, immunophenotyping
• Bone survey (+ whole body low dose CT or MRI in selected cases)
  • NOT dexa
Myeloma

10% clonal population on marrow (or plasmacytoma) +

- CRAB criteria
  - HyperCalcemia
    - Ca+ > 11
  - Renal insufficiency:
    - Cr > 2 (or GFR < 40)
  - Anemia:
    - Hb < 10
  - Bony lesions
    - CT/PET

- ***NEW*** MDEs
  - 60% or greater clonal plasma cells on marrow
  - Serum FLC ratio of >100, with involved light chain >100 mg/L
  - More than 1 MRI bone lesion that is >= 5 mm in size

One or more criteria (either CRAB or MDE) = myeloma
How to remember the new MDEs (unofficial mnemonic)

• **CLAM** criteria
  • **CLonal** (>60% on marrow)
  • **Asymmetric light chains** (ratio > 100)
  • **MRI** (need 2!)
Why did IMWG choose these MDEs?

• Very high risk of progression to CRAB+ myeloma in 2 years
  • Marrow $>60\%$: 95%  (Rajkumar et al, NEJM 2011)
  • Light chain ratio $>100$: 72%  (Larsen et al, Leukemia 2013)
  • $>1$ MRI lesion 70%  (Hillengass et al, JCO 2010)
Who needs CT or MRI for workup?

• “The IWMG now recommends the use of low-dose whole-body CT (LDWBCT) or MRI in the work-up of smoldering multiple myeloma (SMM) and solitary plasmacytoma.”
Smoldering myeloma vs. MGUS

**MGUS**
- Serum monoclonal protein $<$30g/L
- **AND**
- Clonal bone marrow plasma cells $<$10%

**SMM**
- **Serum** monoclonal protein (IgG or IgA) $>$ 30g/L
- **Urinary** monoclonal protein $>$ 500mg per 24h
- and/or **clonal** bone marrow plasma cells 10-60%

In a patient NOT otherwise meeting myeloma criteria
Back to our patient

• 65 y/o M, iron deficiency anemia (mild, Hgb > 10) -> SPEP
  • + TSTQ IgA spike

• Workup:
  • Hgb 11
  • LFCL 171, ratio lambda/kappa 11
  • UPEP w/immunofix negative
  • Bone marrow bx with 10% clonal plasma cells
  • Skeletal survey by XR negative

NEEDS MRI or WBLDCT (these were negative)

**Dx: Smoldering myeloma**
Management of smoldering myeloma

• Serial monitoring **OR**
• Clinical trial
Trials of early therapy in high-risk smoldering myeloma

Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial

Maria-Victoria Mateos, Miguel-Teodoro Hernández, Pilar Gislaña, Javier de la Rubia, Felipe de Arriba, Lucía López Corral, Laura Rosiñol, Bruno Pao, Luis Palomera, Joan Bargay, Albert Oriol, Felipe Prosper, Javier López, José-María Argüitana, Nuria Quintana, José-Luis García, Joan Bladé, Juan-José Lahuerta, Jesús-F San Miguel

Summary

Background The standard of care for smouldering multiple myeloma is observation. We did the QuiRedex study to compare early treatment with lenalidomide plus dexamethasone with observation in patients with high-risk smouldering multiple myeloma. Here we report the long-term follow-up results of the trial.

- “High-risk” myeloma: “We defined high risk as either bone-marrow plasma cell infiltration of at least 10% or presence of monoclonal component (IgG ≥3 g/dL or IgA ≥2 g/dL, or Bence Jones proteinuria >1 g/24 h), or both, plus at least 95% phenotypically aberrant plasma cells in the bone-marrow plasma cell compartment with immunoparesis (reductions in one or two uninvolved immunoglobulins of >25% compared with normal values).”
QuiReDex results

- Other studies pending: stay tuned
Risk factors for progression of smoldering myeloma

• Reviewed in Rajkumar et al, Blood 2015
  • M protein > 30 g/L
  • IgA SMM
  • Clonal BMPCs 50-60%
  • Immunoparesis (reduction of uninvolved isoatypes)
  • FLC ratio 8-100
  • Rising M protein (>25% increase on 2 evaluations within 6 months)
  • T(4;14) or del(17p) or +1q
  • MRI with 1 lesion
IgA smoldering myeloma is particularly high risk for progression

- Kyle RA et al NEJM 2007
- IgA subtype independent risk factor for progression to MM from SMM

Cumulative Risk of Progression to MM from SMM

- 5 year
- 10 year
- 15 year

IgA vs IgM
IgA is difficult to monitor
SPEP

**Electrophorèse des protéines sériques**

<table>
<thead>
<tr>
<th>Protides totaux :</th>
<th>73 g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumine</td>
<td>61.2 g/L</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>4.0 %</td>
</tr>
<tr>
<td>Alpha 2</td>
<td>13.1 %</td>
</tr>
<tr>
<td>Beta</td>
<td>10.5 %</td>
</tr>
<tr>
<td>Gammas</td>
<td>9.2 %</td>
</tr>
</tbody>
</table>

Valeurs normales

<table>
<thead>
<tr>
<th>Protides totaux :</th>
<th>65-190 g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumine</td>
<td>55-70 g/L</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>1.4-4.4 g/L</td>
</tr>
<tr>
<td>Alpha 2</td>
<td>7-9 g/L</td>
</tr>
<tr>
<td>Beta</td>
<td>7-15 g/L</td>
</tr>
<tr>
<td>Gammas</td>
<td>9-18 g/L</td>
</tr>
</tbody>
</table>

Rapport Albumine/Globuline : 1.72
Monoclonal proteins may co-migrate with other serum proteins

e.g. IgA monoclonal protein co-migrates with transferrin

Because of its position, almost half (45%) of IgA patients have non-quantifiable m-spikes
Limitations of electrophoresis

% of non-quantifiable SPE for IgA M-Ig

Adapted from:
Avet Loiseau Hematology Reports 2010;2:G72a; Boyle Blood 2012;120:3970a
Damoiseaux NVVI 2012; Ludwig Leukemia 2013;27:213-9
What Are Hevylite Antibodies?

- **Hevylite recognizes:**
  conformational epitopes between heavy and light chains

- **Can distinguish:**
  - IgAκ v. IgAλ
  - IgGκ v. IgGλ
  - IgMκ v. IgMλ

Must have heavy AND light chain – not a replacement for FLC
Hevylite in IgA myeloma: diagnostic & prognostic

- Boyle et al, Cancer 2014
- 157 patients with IgA myeloma and diagnostic samples
  - SPEP quantifiable in 105/157 cases (67%)
  - All 157 with abnormal HLC ratios
- Isotype paired suppression associated with shortened survival
Hevylite for monitoring

Ludwig et al, leukemia 2013
Hevylite assay continued

- Not yet evaluated as part of diagnostic guidelines

- Kumar et al Lancet Oncol 2016 IMWG response guidelines
  - promising, deserving of future study, not yet ready for primetime
Key Take-Home’s

1) **Revised IMWG Criteria for myeloma**
   - 10% marrow or plasmacytoma plus one CRAB criteria or one MDE
     - MDEs (“CLAM”): Clonality (>60%), asymmetric light chains (>100x), MRI (2 lesions)

2) IgA smoldering myeloma is at high risk for progression

3) IgA can be difficult to monitor - the hevylite assay may have a role – stay tuned
THANK YOU

- Dr. Chauncey

- For your attention