Paraproteinemic Neuropathies
MGUS, Anti-MAG, POEMS,
Dr. Kristine Chapman

Disclosures
• Research support from Genzyme
• Education Project grants from Grifols

Paraproteins are immunoglobulins that are produced in excess by an abnormal clonal proliferation of B-lymphocytes or plasma cells.
Antibody Structure

- Light Chains
  - Lambda
  - Kappa
- Heavy Chains

Paraproteinemnic Neuropathy

- Monoclonal proteins exist as
  - Heavy chain subtypes (mainly IgG, IgA, IgM)
  - Light chain subtypes (kappa or lambda).

Antibody Associated Neuropathies

“The Big Picture”

Neuropathies associated with auto-antibodies
- GBS/CIDP
- Paraneoplastic ie anti Hu antibodies
- Monoclonal proteins
  - MGUS
  - Anti-MAG
  - POEMS
  - Amyloid
  - Cryoglobulinemia
  - CANOMAD syndrome
Protein Electrophoresis and Immunofixation

Paraproteins

- Paraproteins are detected in the serum of
  - 1% of the general population
  - 5% over 70 years of age
  - 10% over 80 years of age

- 10% of patients with a chronic sensory motor neuropathy of unknown origin have an associated serum monoclonal gammopathy

Association with Malignancy

- Clonal proliferation may occur in the context of a hematologic malignancy or a pre-malignancy.

- Associated disorders include
  - Multiple myeloma
  - Cryoglobulinemia
  - Lymphoma
  - Amyloidosis
  - Waldenstrom macroglobulinemia
  - POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein spike, and skin manifestations) syndrome
### Defining Features of Common B-Cell Clonal Disorders

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Symptomatic</th>
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<tbody>
<tr>
<td>MGUS</td>
<td></td>
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<tr>
<td>Serum Lambda</td>
<td>&lt; 10 mg/L</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>&lt; 20 mg/L</td>
</tr>
<tr>
<td>Serum light chain</td>
<td></td>
</tr>
<tr>
<td>Light chain</td>
<td>monoclonal</td>
</tr>
<tr>
<td>Serum free light chain</td>
<td></td>
</tr>
<tr>
<td>0% kappa</td>
<td></td>
</tr>
<tr>
<td>Sensory level</td>
<td>to mid-shin</td>
</tr>
<tr>
<td>Weakness</td>
<td>EHL 4+/5</td>
</tr>
<tr>
<td>Absent ankle jerks</td>
<td></td>
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<tr>
<td>NCS: sensory-motor axonal neuropathy</td>
<td></td>
</tr>
<tr>
<td>Serum Immunofixation shows Ig G kappa (1 g/dL)</td>
<td></td>
</tr>
</tbody>
</table>

### Case #1- MGUS

- 73 year old African-Canadian man with a 9 month history of numbness and paresthesias in the feet
- Sensory level to the mid-shin
- Weakness of EHL 4+/5, otherwise normal
- Absent ankle jerks
- NCS: sensory-motor axonal neuropathy
- Serum Immunofixation shows Ig G kappa (1 g/dL)

What to do About MGUS?
“MGUS”
Monoclonal Gammopathy of Uncertain Significance

- MGUS is a common, age-related condition.
- Accumulation of plasma cells from a single abnormal clone without proliferation of malignant cells.
- Usually asymptomatic.

- Three criteria define MGUS:
  - A monoclonal paraprotein band < 10 g/L (3 g/dL)
  - Plasma cells < 10 % on bone marrow
  - No evidence of end organ damage: “CRAB”
    - Hypercalcemia
    - Renal insufficiency related to the paraprotein
    - Anemia
    - Bone lesions

- (If they have a neuropathy, they are already “of interest” – not incidentally found)

MGUS → Transformation

- Each year 1% of people with MGUS go on to develop a more serious disorder

Risk Stratification in MGUS

- Monoclonal protein > 1.5 g/dL
- Ig A or Ig M (non IgG)
- Abnormal Free Light Chain ratio
  - Kappa-Lambda ratio < 0.26 or > 1.65 is abnormal

- 1 risk factor: Low risk 5% progression in 20 years
- 2: Intermediate risk 20% progression in 20 years
- 3: High risk 60% progression in 20 years
MGUS Work UP

- Hx and physical (fatigue, bone pain)
- CBC
- Routine chemistry (calcium, GFR, creatine, albumin, LFT)
- SPEP /UPEP
- Immunofixation
- Serum-free light chain assay
- Urinalysis - protein/creatinine ratio
- Skeletal survey
- Hematology review → bone marrow biopsy

Advise GP to see twice annually initially, low risk can reduce to annual f/u.
For intermediate and high risk the hematologist will often follow as well.
Only repeat imaging or bone marrow analysis if suspicion of progression.

Testing strategy

- Characterize the neuropathy: NCS/EMG
- CSF analysis — elevated protein, cytology for leptomeningeal infiltration (in presence of lymphoma)
- Nerve and muscle biopsy — exclude infiltrative neoplasm, vasculitis or AL
- VEGF for POEMS — Vascular endothelial growth factor

MGUS Screening

MGUS treatment

- Rx if assoc. with CIDP
- Treat neuropathic pain
- ETOH moderation
- Remain active
- Foot checks
- OT/PT as needed

M. Brigden, BC Medical Journal, vol. 56 2014
CASE 2: Anti-MAG Neuropathy

- Fit 49 yr ER physician, runs weekly
- Bilateral burning and numbness in soles of feet, sensation of bunched socks, tripping, bilateral hand tremor with some difficulty suturing lacerations in ER

**Case 2: Anti MAG Neuropathy**

- **PE:**
  - Mild wasting of hand and intrinsic foot muscles, distal weakness
  - Absent ankle jerks
  - Impaired position sense in toes, vibration loss in toes and hands
  - Ataxic gait
  - Tremor.

- **DX:** sensorimotor PN presenting with distal weakness and sensory findings

- **Lab:** CBC, FBG, B12 normal.
  - Monoclonal IgM kappa band 15.2 g/L

**Electrodiagnostic Findings**

- Long distal latencies

<table>
<thead>
<tr>
<th>Name</th>
<th>Lat</th>
<th>DIU</th>
<th>Aner P-P</th>
<th>Aner D-P</th>
<th>Amplitude</th>
<th>Temp</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Peroneal Motor Left</td>
<td>19.9</td>
<td>19.9</td>
<td>1.35</td>
<td>0.84</td>
<td>99.0</td>
<td>93.0</td>
<td></td>
</tr>
<tr>
<td>Tibialis Anterior</td>
<td>20.0</td>
<td>20.0</td>
<td>1.39</td>
<td>1.30</td>
<td>93.0</td>
<td>99.0</td>
<td></td>
</tr>
<tr>
<td>A. Tibialis Posterior</td>
<td>20.0</td>
<td>20.0</td>
<td>1.37</td>
<td>1.32</td>
<td>76.0</td>
<td>71.0</td>
<td></td>
</tr>
</tbody>
</table>
Case 2: DADS with IgM paraproteinemia

- Positive anti-MAG assay at Athena
- RX: Rituximab
- 2 year later – function excellent running 30 km/wk, hand tremor and manual dexterity improved continues to work as ER physician
- Persistent neuropathic pain in extremities improved with neuropathic pain treatment

DADS Phenotype

“Distal Acquired Demyelinating Symmetric”

- Increased prevalence in men, age > 50
- Predominantly distal sensory loss
- Mild distal weakness
- Hand tremor
- Unsteady gait
- IgM paraproteinemia (present in 2/3) 
  → Anti-MAG antibodies
- Subgroup has an indolent presentation - follow clinically
- Poor response to immunosuppressive
  — Rituximab, PLEX, cyclophosphamide

Case 3 - POEMS

- 56 year-old male
- Feb 2015:
  — Burning dysesthesias. Worse at night
  — Numbness and tingling in feet
  — Slowly progressed over months to below knees
- Nov 2015:
  — Similar symptoms in fingers
  — Hand tremor
- Jan 2016
  — Erectile dysfunction (low testosterone)
Neurological exam

- Normal cranial nerves.
- Strength:
  - 4+ weakness on EHL and toe extensors
- Sensory examination
  - Decreased temperature, pinprick, and light touch to mid tibia and elbow
  - Absent vibration at the ankles
- Mild postural tremor in hands

Previous Investigations

- CBC: thrombocytosis
- Elevated fasting Glucose.
- Normal protein electrophoresis.
- Electrolytes, kidney function, TSH, ANA, ANCA, ENA, RF, Vitamin B12, syphilis
- Previous NCS: reported as axonal PN.

EMG/NCS

<table>
<thead>
<tr>
<th>Sensory Nerve Conduction Studies</th>
</tr>
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<tbody>
<tr>
<td>Nerve</td>
</tr>
<tr>
<td>Median - Right</td>
</tr>
<tr>
<td>Ulnar - Left</td>
</tr>
<tr>
<td>Superficial Peroneal - Right</td>
</tr>
<tr>
<td>Lateral Poplite - Left</td>
</tr>
<tr>
<td>Superficial Radial - Right</td>
</tr>
<tr>
<td>Ulnar - Medial</td>
</tr>
<tr>
<td>Median - Medial</td>
</tr>
<tr>
<td>Median - Right</td>
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<tr>
<td>Ulnar - Left</td>
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</table>
Demyelinating neuropathy but axonal involvement more common than CIDP

Skin Changes

• On general exam:
  – Cherry red angiomas in chest
  – Leg discoloration

Endocrine Changes

• Erectile dysfunction → recent diagnosis of hypogonadism, on hormone replacement
More labs

• Serum Proteins
  – Normal Ig levels
  – Small band (approx. 1.2 g/L) in the fast gamma region.
  – Immunofixation: monoclonal IgA lambda
  – Free Light Chains normal
  – Kappa/Lambda ratio normal

• Hormones
  – Testosterone low
  – Cortisol N
  – Prolactin elevated

Skeletal survey

• No destructive bone lesions

• Sclerotic focus on distal right femur interpreted as a “small bone island”

Abdominal US

• Splenomegaly

• No hepatomegaly or lymphadenopathies
Bone Marrow Biopsy

- Polyneuropathy
- Organomegaly: splenomegaly
- Endocrinopathy: hypogonadism, impaired fasting glucose
- M-protein: IgA Lambda
- Skin: cherry red angiomas, skin discoloration
POEMS syndrome

- Papilledema
- Extravascular Fluid Overload
- Sclerotic Bone Lesions
- Thrombocytosis or polycythemia
- Respiratory dysfunction
- Increased risk of thrombosis

Elevated VEGF

- The cytokine VEGF correlates best with disease activity and is markedly increased in POEMS
- Increases vascular permeability, targets endothelial cells, and is important in angiogenesis.
- A plasma VEGF level of 200 pg/mL or greater has a specificity of 95% and sensitivity of 68% for POEMS

Autologous Stem Cell Transplant

- Higher chance of hematologic complete response
- Associated with significant PN improvement:
  - No need of wheelchair, improvement in NIS and mRS
  - Initial improvement by 3 months, max at 3 years
- No correlation between severity of PN and VEGF levels at baseline
  - But VEGF response to treatment associated with hematological and neurological response
Case 3: Before POEMS Dx

- Received 3mo IVIG and oral steroids
  - Improvement in pain.
  - Worsened strength

POEMS Treatment

- Autologous stem cell transplant

Conclusion

- Paraproteinemic neuropathy: characterized by the presence of homogenous immunoglobulin in serum.
  - If malignancy is identified, target treatment to neoplasm
- Most cases are MGUS
- Anti MAG neuropathy → treat if disabling; rituximab
- POEMS syndrome → autologous stem cell transplant
- Multidisciplinary collaboration needed!
## Paraproteinemic Neuropathy

<table>
<thead>
<tr>
<th>Hematologic Disorder</th>
<th>Most Common Monoclonal Protein Type</th>
<th>Peripheral Neuropathy Monotype</th>
<th>Electrodagnostic Monotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin M monoclonal gammopathy of undetermined significance (IgM MGUS)</td>
<td>IgM kappa</td>
<td>Distal large fiber sensory predominant neuropathy with sensory ataxia</td>
<td>Denervating with prolonged distal latencies</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>IgM kappa</td>
<td>Distal large fiber sensory predominant neuropathy with sensory ataxia</td>
<td>Axonal greater than demyelinating, both proximal distal</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>IgG more often than IgA</td>
<td>Length-dependent sensory, sensorimotor or motor neuropathy</td>
<td>Axonal</td>
</tr>
<tr>
<td>Polynyurhythmia, organ myeloma, endoneuropathy, monoclonal plasma cell disorder, and skin changes (PMN syndrome)</td>
<td>IgG or IgA, lambda</td>
<td>Sensory motor polyneuropathy with chronic inflammatory demyelinating polyneuropathy</td>
<td>Axonal</td>
</tr>
<tr>
<td>Immunoglobulin light chain (AL) amyloidosis</td>
<td>Lambda</td>
<td>Sensory motor peripheral neuropathy with prominent autonomic neuropathy</td>
<td>Axonal</td>
</tr>
</tbody>
</table>