Case presentation

Polyneuropathy and a paraprotein
small clone – big problem

ESIM Winterschool – jan 2013

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The Netherlands
Case history:
60 year old man  with pain and swelling of the feet

• 2011:
  Pain in both feet, accompanied by swelling of the feet/ankles.
  Blue-ish discoloration of the hands.

• Evaluated by several specialists in “St. Elsewhere”:
  – rheumatologist: diagnosis “arthralgia of unknown origin”
  – vascular surgeon: no diagnosis
  – neurologist: no diagnosis

• 2012:
  Facial rash. Biopsy: “lupus-like skin reaction”.
  Receives topical corticosteroid.
  Again referral to rheumatologist. Conclusion: no systemic LE.
Case history:
60 year old man with pain and swelling of the feet

- **2012:**
  Progressive difficulty walking and getting up stairs (leg weakness).
  Reduced sensation in feet.

- **EMG:**
  Multifocal demyelinating disease causing sensory and motor neuropathy

- **Protein electrophoresis:** monoclonal band

- **Referred to hematologist for further analysis**
Paraprotein & polyneuropathy
- a differential diagnosis
Paraprotein & polyneuropathy - a differential diagnosis

- Multiple Myeloma
- MGUS

- Specific syndromes:
  - Amyloidosis
  - POEMS syndrome
  - Waldenstrom’s disease
  - IgM related polyneuropathy, e.g. anti-MAG associated
  - CANOMED syndrome
    - Chronic Ataxic Neuropathy
    - Ophthalmoplegia
    - M-protein (IgM)
    - cold agglutinins
    - Cisialosyl (anti-ganglioside anti-GD1b and anti-GQ1b) antibodies
Paraprotein & polyneuropathy - a differential diagnosis

- Multiple Myeloma
- MGUS

- Specific syndromes:
  - Amyloidosis
  - POEMS syndrome
  - Waldenstrom’s disease
  - IgM related polyneuropathy, e.g. anti-MAG associated
  - CANOMED syndrome

In this patient: **IgA-lambda** paraprotein *small non quantifiable band* with normal kappa / lambda free light chains
POEMS syndrome – diagnostic clinical criteria

**Mandatory criteria** *(both required)*
- Polyneuropathy
- Monoclonal plasmaproliferative disorder

**Major diagnostic criteria** *(1 required)*
- Vascular endothelial growth factor (VEGF) level elevation
- Sclerotic bone lesions
- Castleman’s disease

**Minor diagnostic criteria** *(1 required)*
- Organomegaly
- Extravascular volume overload
- Endocrinopathy
- Skin changes
- Papilledema
- Thrombocytosis / polycythemia

**Other symptoms**
- Clubbing, hyperhidrosis, pulmonary hypertension, restrictive lung disease, thrombotic diathesis, diarrhea, low vitamin B12 levels
Physical examination: “lupus like skin eruption”
Physical examination: acrocyanosis
Physical examination:
hyperpigmentation & hypertrichosis
Physical examination:
Peripheral pitting edema
Laboratory testing

- IgA-lambda paraprotein – detectable, but non-quantifiable
  Free light chain levels and - ratio normal
  Beta-2-microglobulin increased (4.2 mg/l)
- Marginal thrombocytosis (434 x10⁹/l) with otherwise normal CBC
- Routine chemistry and electrolytes all within normal limits
- Endocrinological testing:
  - Hypogonadism with testosterone level of 5.3 nmol/l (ref 7.0-31)
  - Adrenal insufficiency:
    - Morning cortisol level 0.27 µmol/l
    - ACTH-test: maximum peak 0.39 µmol/l (ref >0.50 µmol/l)
- VEGF: 17156 pg/ml (ref 10 – 150)
- Vitamin B12: 81 pmol/l (ref 130-700)
CT-whole body: multiple sclerotic bone lesions + (modest) splenomegaly
Ophthalmologist: bilateral papilledema (asymptomatic !)
Making the diagnosis:
Some subtle, but all there!

**Mandatory criteria (both required)**
- Polyneuropathy +
- Monoclonal plasmaproliferative disorder +

**Major diagnostic criteria (1 required)**
- Vascular endothelial growth factor (VEGF) level elevation +
- Sclerotic bone lesions +
- Castleman’s disease -

**Minor diagnostic criteria (1 required)**
- Organomegaly +
- Extravascular volume overload +
- Endocrinopathy +
- Skin changes +
- Papilledema +
- Thrombocytosis / polycythemia +

**Other symptoms**
- Clubbing, hyperhidrosis, pulmonary hypertension, restrictive lung disease, thrombotic diathesis, diarrhea, low vitamin B12 levels +
To fight the clone, find it we must...
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>Cytomorphology</td>
<td>1 % plasma cells (normal)</td>
</tr>
<tr>
<td>Immunophenotyping (flow cytometry)</td>
<td>0.09% plasma cells</td>
</tr>
<tr>
<td></td>
<td>all polyclonal</td>
</tr>
<tr>
<td>Histology</td>
<td>5% plasma cells</td>
</tr>
<tr>
<td></td>
<td>polyclonal</td>
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</tbody>
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Peripheral blood immunophenotyping

0.004% of nucleated cells are circulating plasma cells

No kappa/lambda restriction: polyclonal!
Osteosclerotic lesions: FDG-PET-negative!
(in our patient)
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>Sep 2012</td>
<td>diagnosis hydrocortisone + testosterone + vitamin B12 supplementation</td>
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<tr>
<td></td>
<td>stem cell apheresis after 5 days G-CSF</td>
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<tr>
<td>Oct 2012</td>
<td>high-dose melphalan (2 days 100mg/m2)</td>
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<tr>
<td></td>
<td>autologous stem cell transplantation</td>
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<tr>
<td>Nov 2012</td>
<td>hospital admission with neutropenic fever repopulated</td>
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<tr>
<td>Dec 2012</td>
<td>slow recovery – fatigue, poor performance</td>
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<tr>
<td>Jan 2013</td>
<td>improving general health</td>
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<tr>
<td></td>
<td>no further progression of polyneuropathy</td>
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<tr>
<td></td>
<td>IgA-lambda band no longer detectable</td>
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What I learnt from this case

• Small plasma cell clones can cause major disease
  
beware of a small IgA-lambda band
  in a polyneuropathy patient!

• Knowing what to look for makes you see
Additional slides for discussion
CLONAL PLASMA CELLS ON ILIAC CREST BIOPSY?

Yes

> 3 bone lesions

Yes

Systemic therapy

No

Yes or No

Vigorous supportive care

No

Curative doses of radiation to affected site(s)

Extensive assessments every 3-6 months

Figure 1. Algorithm for the treatment of POEMS syndrome.

Dispenzieri et al. Blood 2012
**Systemic therapy**

**1st choice:**
high dose melphalan + autologous stem cell transplantation

**Alternatives:**
- Intermediate dose melphalan
- Melphalan / dexamethasone
- Thalidomide / dexamethasone
- Lenalidomide / dexamethasone (/ cyclophosphamide)
- Bortezomib / dexamethasone

Dispenzieri et al. Blood 2012
“Pathological paraprotein”, nearly always lambda clone. IgG or (often!) IgA

Exact pathogenesis of the disease is unclear

High circulating levels of cytokines IL-1, IL-6, VEGF, and TNF
Low circulating levels of cytokine TGF-β

VEGF-inhibition alone (bevacizumab) ineffective