Paraproteins, MGUS and Myeloma

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Talk Outline

– Biology of plasma cells and paraproteins
– Laboratory Tests and interpretation
– When to request protein electrophoresis
– How to deal with a positive result
– When to refer
– Management of MGUS in the Community
– Myeloma prognosis and treatment: The basics
Myeloma is a malignancy of plasma cells
Plasma cells are terminally differentiated B cells
Plasma cells produce specific antibodies
Antibodies
Plasma cell development
Laboratory Tests for a Monoclonal Protein:
1. Serum Protein Electrophoresis

Lane 3 – IgA kappa paraprotein 28 g/L
Lane 2 – IgM kappa paraprotein 8 g/L
Lane 3 – IgG lambda paraprotein 7 g/L
Laboratory Tests for a Monoclonal Protein: Immunofixation
Laboratory Tests for a Monoclonal Protein: Serum Free Lightchains (Freelites)
Laboratory Tests for a Monoclonal Protein: Urine Protein Electrophoresis

- Positive or negative for Bence Jones Protein (BJP) which are just free light chains which have undergone glomerular filtration
When to Test for a Monoclonal Protein

- Raised ESR or plasma viscosity
- Unexplained anaemia, hypercalcaemia or renal failure
- Raised total protein/globulins
- Reduction of one or more immunoglobulin class levels (IgG, IgA, IgM)
What to Request

– FBC
– U+E
– Calcium
– Serum protein electrophoresis
– Urine protein electrophoresis or serum freelight chains
How to interpret a positive result

- Monoclonal proteins can be associated with:
  - MGUS
  - Myeloma
  - Solitary Plasmacytoma
  - AL amyloidosis
  - Waldenstrom’s Macroglobulinaemia
  - Low grade B-NHL and other B-cell LPDs
  - Rare disorders caused by paraprotein damage (usually neurological)
How to Investigate a Positive Result: Take a History for Signs/Symptoms of Myeloma, Lymphoma/LPD and Amyloidosis

- **Myeloma**
  - Bone/back pain
  - Anaemia
  - Renal impairment
  - Hypercalcaemia
  - Hyperviscosity

- **Lymphoma/LPD**
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Hyperviscosity
  - Anaemia
  - B symptoms (sweats, unexplained weight loss)
How to Investigate a Positive Result: Take a History for Signs/Symptoms of Myeloma, Lymphoma/LPD and Amyloidosis

- **Amyloidosis**

- Macroglossia
- Unexplained cardiac failure
- Nephrotic syndrome
- Peripheral neuropathy
- Carpal tunnel syndrome (often bilateral)
When to Refer to Haematology

- Signs or symptoms of myeloma, lymphoma or amyloidosis
- Significant BJP (>500 mg/L)
- IgD or IgE M-proteins
- IgG PP >15 g/L
- IgA or IgM PP >10 g/L
The Majority of Patients will have MGUS
(monoclonal paraprotein of undetermined significance)

- Paraprotein $< 30$ g/L
- Plasma cells $< 10\%$ in bone marrow
- No myeloma associated organ damage (bone marrow failure, hypercalcaemia, renal impairment, bone destruction)
Prognosis of MGUS

- Associated with increased risk of malignant transformation
- Also associated with osteoporosis and DVT
- Risk of malignant transformation can be stratified based on level of PP, isotype of PP and sFLC ratio
- Higher risk of progression associated with non-IgG isotype, PP > 15 g/L and abnormal sFLC ratio
## MGUS - risk of progression

- Mayo risk model
- 1 point for non-IgG isotype, PP > 15 g/L and abnormal sFLC ratio

<table>
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<th>Number of risk factors</th>
<th>Risk category</th>
<th>20 year progression risk (%)</th>
<th>20 year risk accounting for death as a competing factor (%)</th>
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<td>3</td>
<td>High</td>
<td>58</td>
<td>27</td>
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Management of MGUS in the community

- 4 monthly tests for the first year
- Then reduced to 6-12 monthly if stable
- Tests should include:
  - FBC
  - U+E
  - Calcium
  - Serum protein electrophoresis
  - Serum free light chains
Myeloma - Epidemiology

- 5000 new cases in the UK per year
- 10-15% of all haematological malignancies
- Incidence increases with age – average age at diagnosis 70
- 40% of patients present aged <60 years
- 1 – 2% aged <40 years
- More common in men than women (60:40)
- Racial differences in incidence (twice as common in black compared with caucasian, less common if of Asian origin)
Myeloma: Presentation
1. Bone marrow failure

- Anaemia (usually normocytic, sometimes macrocytic)
- Neutropenia and thrombocytopenia are less common
Myeloma: Presentation
2. Bone pain

- Back pain is most common
- Any bone in the axial skeleton can be affected – ribs are another common site of pain
- 3% of patients present with spinal cord compression
Myeloma: Presentation
3. Renal Failure

- Usually cast nephropathy due to high light chain load
- Often exacerbated by hypercalcaemia, NSAID use
- Light chain deposition and amyloid deposition are rarer causes
Myeloma: Presentation
4. Infection

- Pneumonia is most common
- Nearly all patients have immune paresis at presentation (suppression of normal immunoglobulins)
Myeloma: Presentation
5. Hypercalcaemia

- Due to bone lysis
- Causes renal failure, abdominal pain, constipation and confusion
Myeloma - prognosis

Net Survival – England and Wales 2010-11
Myeloma - Prognosis Change over time

1 year survival

5 year survival
Myeloma Treatments

- **Drugs**
- Radiotherapy (to pathological fractures, spinal cord compression and for palliation of pain for focal lesions)
- Bisphosphonates (zoledronic acid) – for fracture prevention, prevention of hypercalcaemia
- Aggressive treatment of infections, especially in the first 6 months
Myeloma Treatment: Chemotherapies

- Alkylating Agents
  - Melphalan
  - Cyclophosphamide
- Corticosteroids
  - Dexamethasone
  - Prednisolone
- Immunomodulatory Drugs
  - Thalidomide
  - Lenalidomide (Revlimid)
  - Pomalidomide
- Proteasome inhibitors
  - Bortezomib (Velcade)
  - Carfilzomib
Myeloma Treatment: Chemotherapies

- Histone deacetylase inhibitors
  - Panobinostat
- Monoclonal antibodies
  - Daratumumab
Myeloma Chemotherapy: General Concepts

- Usually combine agents with triplet therapy (e.g. VTD (velcade, thalidomide and dexamethasone))
- Treat until maximum response (based on biochemical marker)
- Younger, fitter patients will receive an autologous stem cell transplant
- Usually stop treatment once maximum response is reached
- Increasing evidence for ongoing therapy (maintenance)
Myeloma Therapy: Future Directions

- Immunotherapies
  - checkpoint inhibitors
  - CAR-T therapy
Scenario

- 79 year old man
- No concerning symptoms
- Routine blood tests
  - Hb 129 g/L
  - MCV 99
  - WBC, Plt normal
  - U+E, calcium normal
  - IgG kappa paraprotein of 9 g/L
  - sFCL: kappa 79 mg/L, lambda 10 mg/L, ratio 7.9