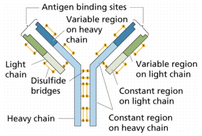
MULTIPLE MYELOMA

Multiple myeloma

- Immunoglobulins (Ig) = Antibodies.
- They are proteins made by plasma cells.
- Plasma cells develop from B lymphocytes.
- Plasma cells usually make lots of different types of antibodies.
- But sometimes as it changes from a B lymphocyte to a plasma cell, it becomes cancerous.
- And starts to produce large amounts of a single antibody, which are known as paraprotein or monoclonal antibody (M-spike / M-protein).

- Antibodies are made up of heavy chains and light chains.
- Heavy chains are IgM, IgG, IgA etc.
- The light chains are kappa and lambda.
- Hence, can describe an antibody as an IgA kappa or an IgG lambda.
- Commonest is IgG and IgA myeloma.



- Antibodies are in the gammaglobulin class of proteins.
- So if you use electrophoresis you separate the gamma-globulins out into different sub types.
- As proteins are -vely charged they move down the plate towards the +ve charge, and the smaller one's will move faster and hence, separate out.
- But all this tells you is that the pt has lot's of gammaglobulins.
- It doesn't tell you which type e.g. IgA, IgG, IgM, kappa, lambda etc
- The same occurs with the urine electrophoresis. It just shows the gammaglobulin as Bence Jones Protein. But doesn't tell you which subtype.
- The serum and urine electrophoresis are quantitative, not qualitative tests.

- To determine the subtype, you need serum immunofixation electrophoresis.
- This will tell you it's IgG or IgM or kappa etc
- Urine immunofixation electrophoresis tells you if it is kappa or lambda.

Disclaimer:
Read the disclaimer at medimaps.co.uk/disclaimer

References:
1. cks.nice.org.uk
2. Heart of England haematology department shared care protocol
3. Dr Shankara Paneesha haematologist consultant, Heart of England Mar 2017.
4. Dr Craig Hofmeister, Learn about multiple myeloma, Youtube.
5. Early detection of multiple myeloma in primary care using blood tests: a case control study in primary care, BJGP 2018.
6. Patient.co.uk
7. Dr Anastasia Chew haematology consultant Feb 2022.

Symptoms

- hyperCalcaemia >2.6 mmol/L
- imapired Renal function eGFR < 40 or Cr > 176
- Anaemia Hb <10
- Bone lytic lesions or #

- Back pain, rib pain, chest pain.
- Chest infections.
- SOB.
- Headache
- Epistaxis.
- #.
- Wt loss.
- Nausea.

- One of the worst in terms of delays in diagnosing by GP's. Because early symptoms are vague.
- Many of the symptoms occur in late disease.
- Hence, importance of investigations.

Investigations

- FBC.
- UEs.
- Calcium.
- LFTs.
- ESR (CRP not useful).
- Ig.
- Xray to look for lytic lesions.
- Urine Bence jones protein.

- Ig increase the total protein levels in the blood.
- But the albumin falls due to inflammatory mediators e.g. cytokines.

- >65y male = normal upper limit = age / 2.
- >65y female = (age + 10) / 2.

* See below for how to interperate.

- Limited role now that we have serum free light chain.
- The malignant light chains spill fromthe blood and into the urine.
- ↓ renal function can ↓ clearance of light chains.
- So Kappa and Lambda can be high, but if ratio is normal then does not mean myeloma.

- Normal Hb and ESR = 93% sensitivity to rule out myeloma.

Management

- Refer to haematology for confirmation e.g. bone marrow biopsy.
- Referral should be either 2ww or routine.
- Which to choose?

2WW =
- Monoclonal paraprotein > 10 g.
- ↑ serum free light chains with abnormal ratio > 5 or < 0.1.
- Urine BJP suggesting myeloma.
- Paraprotein of any level in the presence of any:
- Unexplained abnormal FBC, UEs, bone profile.
- Red flag symptoms i.e. cauda equina syndrome.

ROUTINE =
- Abnormal paraprotein but not meeting 2ww criteria.

- Ig G > 15g/L, Ig A or Ig M >10g/L
- Any level Ig D or Ig E paraprotein.

-???
- Contradictory guidance re: Ig levels
- NW guidelines Vs haem consultant showing criteria on when to refer 2ww
- Consultant had it as urgent, NW has it as routine.

Immunoglobulin result interpretation

- There are 3 different tests which are often lumped together:
- Immunoglobulins electrophoresis (tells you quantity).
- Immunoglobulin immunofixation (tells you subtype)
- Serum free light chains (tells you ??? of light cain)

??? the quantity
??? the subtype

- Polyclonal increases are not myeloma or MGUS. They are likely a reactive increase i.e. non-specific immune reaction.
- Sometimes myeloma cells are crippled so do not produce whole antibodies, rather only produce light chains. So for these we would see only kappa or lamda at high levels. Hence, the ratio will be high. Which implies a clonal expansion of a plasma cell i.e. myeloma risk.
- Whilst you can have myeloma without a paraprotein (1% may be totally non-secretory or just secreting light chains into blood or urine), you can't have myeloma without immuneparesis.
- Immuneparesis = all the immunoglobulins at low numbers except the one with the paraprotein. Implies you have lost your normal plasma cells and you are not producing normal antibodies, and you are at high risk.
- Commonest is IgG and IgA myeloma.
- Polyclonal IgA seen in chronic liver disease and chronic infections.
- Incidentally low IgM alone is common and rarely clinically important.

Serum free light chains SFLC i.e. kappa and lambda:

- If both are high it's less concerning as we are looking for a single plasma cell that has mutated into a Ca and is producing a single light chain i..e either kappa or lamda. So if both are high it does not fit with a picture of myeloma.
- Can be ↑ in a variety of conditions.
- Repeat one off borderline abnormalities i.e. do not panic refer.
- Refer if kappa or lambda > 200mg/ml.
- If ratio >4 or < 0.25 refer as 2ww.
- Both kappa and lambda light chains are cleared by the kidney's, hence, renal impairment can ↑ levels.
- The proposed SFLC ratio reference range in these pts is 0.37-3.10

Smouldering myeloma

- More advanced pre-malignant stage compared to MGUS.
- Progresses to myeloma 10% per year over the first 5yrs, less thereafter.

Symptoms

- Asymmptomatic

- Monoclonal protein ≥30 g/L.
- Monoclonal plasma cells in bone marrow 10-60%.
- Absence of myeloma-defining organ or tissue impairment.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- How common is it:
- 1% > 50y.
- 10% > 80y.

- Risk of progression to myeloma is 1% per year.

- Three subtypes:
- Non IgM MGUS.
- IgM MGUS.
- Light chain MGUS.

Symptoms

- Asymmptomatic

- Monoclonal protein <30 g/L.
- Monoclonal plasma cells in bone marrow <10%.
- Absence of myeloma-related organ or tissue impairment.

Investigations

- Monitoring blood tests every 6/12.

- FBC.
- UEs.
- Calcium.
- Paraprotein level (monoclonal band).
- Serum free light chain.

refer back to haematology if any of following:

- Unexplained anaemia (drop in Hb of 20 from baseline, or <100).
- Unexplained thrombocytopenia (drop in plt < 100).
- Unexplained neutropenia (<1.5).
- Lymphocytes are doubling in number over <6/12.
- Unexplained cytopenias.
- Rapid rise in paraprotein level or serum free light chains.
- Localised pain in back, ribs or long bones.
- Significant ↑ Cr from baseline, or Cr>115 (when previously normal with no other cause).
- Unexplained elevated calcium.
- Bulky lymph nodes or organomegaly.
- B symptoms.

- If 2 consecutive readings show > 25% rise in paraprotein or serum free light chain.
- The absolute ↑ paraprotein should be > 5g.
- The absolute ↑ serum free light chain should be > 100.