

Myeloma

- Presence of malignant plasma cells in the bone marrow
- Most often secrete a monoclonal immunoglobulin(s) or fragments of immunoglobulin
- May also be non-secretory (~1%).
- Presence of paraprotein is part of diagnostic criteria.
- Typed according to paraprotein (see below for percentages).
- **β2-microglobulin** is best prognostic marker at diagnosis.
- Can monitor by measuring paraprotein concentration, if present.
 - Frequency according to clinical condition and treatment.
- Monitor bone metabolism. Treated with bisphosphonates.
- Consider clinical effects of paraprotein (see below)

Paraprotein types generally & in myeloma

Type	Paraproteins	Myeloma
IgG	53%	53%
IgA	22%	22%
IgM	11%	0.5%
IgD	1%	1.5%
IgE	<0.001%	0.1%
BJP only	12%	21%
Non-secretory	-	1%

Causes of paraproteinaemia

Waldenstrom's macroglobulinaemia

- IgM paraprotein associated with hyperviscosity
- Pentameric IgM (macroglobulin) paraprotein can cause hyperviscosity
- May have impaired clotting function.
- Malignant B cells usually in the lymph nodes or spleen.

MGUS

- Paraprotein with no apparent clinical effects.
- Initially recheck in 3-6 months.
- May be persistent or transient.
- Can be incidental findings in the elderly (up to 7% in 9th decade).
- **Persistent:** Monitor annually, approx. 1% per year may progress to a B cell malignancy.
- **Transient:** Associated with a response to infection, or seen post bone marrow/stem cell transplant.

CLL

- Raised WCC due to malignant B cells.
- May be associated with a paraprotein.

What is it called?

Monoclonal protein is appropriate name. Paraprotein commonly used in UK. M component/protein used in US.

KEY: Paraprotein ≠ B cell malignancy

(Detecting a paraprotein does not necessarily mean that the patient has a B cell malignancy).

Lymphoma

- Presence of malignant B cells in the lymph nodes or spleen
- **Hogkin's lymphoma** (presence of Reed Sternberg cells) or **non-Hodgkin's lymphoma (NHL)** typed according to the phenotype of the malignant B cells.
- May be associated with a paraprotein, usually IgM.

Cryoglobulinaemia

- Presence of a paraprotein that precipitates in the laboratory when incubated at 4C and dissolves when returned to 37C.
- **Type I cryoglobulinaemia** consists of a paraprotein, usually IgM but may also be IgG (IgG3) or IgA.
- Symptoms are due to the protein precipitating in cold extremities in vivo.
- Can cause ischaemia, necrosis and may lead to sepsis, loss of tissue and possibly even require amputation (of fingers or toes).
- See Renal poster for other cryoglobulins.



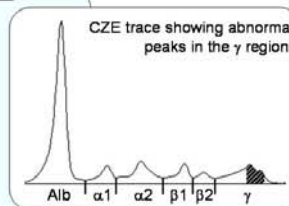
Type I cryoglobulin (Sample is gel-like)

B CELL MALIGNANCY

Laboratory investigation of B cell malignancy

Step1: Electrophoresis

- **Protein electrophoresis** of serum
 - gel or capillary zone electrophoresis (CZE)
- Protein electrophoresis of urine (gel)
 - 2nd void of day ideal, 24h urine not essential
- Quantify serum **immunoglobulin concentrations**
 - Electrophoresis results cannot be interpreted without these.



- Paraprotein is at sufficiently high concentration to increase the viscosity of the blood.
- Puts pressure on circulation
- Capillaries can rupture (can be seen by looking at the capillaries in the back of the eye)
- May also cause splinter haemorrhages
- May interfere with clotting function.

2. Hyperviscosity

Symptoms:

- Headache
- Lethargy
- Blurred vision
- Retinopathy
- Confusion

Step2: Immunofixation

- Immunofixation of any samples where an abnormality is seen.
- Have a low threshold for immunofixation:
 - Any abnormalities on electrophoresis, no matter how minor.
 - Unexplained immune suppression in an adult.
 - Paraprotein in urine but no obvious serum band.
 - Known patient and paraprotein no longer visible
- Remember immunofixation (but not immunosubtraction) is a more sensitive method
- Remember to check for D and E if only monoclonal light chain is detected on serum immunofixation.
- Consider fragments e.g. retained BJP in the serum, heavy chain disease.

Analysis of immunoglobulins is **ONLY** useful for investigating immune deficiency or B cell malignancy.

3. Amyloidosis

A group of diseases where abnormal proteins self-assemble into insoluble fibrils (**AMYLOID**) which deposit in the extracellular space of tissues, impairing function.

What is amyloid?

- An insoluble substance that is resistant to proteolytic degradation.
- Formed when abnormal proteins self-assemble into insoluble fibrils.
- Many different types of amyloid e.g. AL amyloid = monoclonal light chains i.e. Bence Jones protein. e.g. AA amyloid = serum amyloid A.

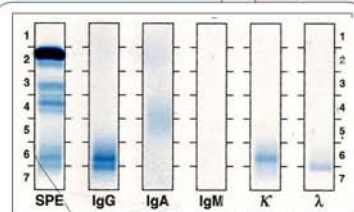
AL amyloidosis

- Patients with Bence Jones protein are at risk of AL amyloidosis.
- Particularly affects the kidney, causing renal failure
- Also deposits in spleen and heart.
- Deposition in heart a big problem because:
 1. Kidney function can be supported but cardiac function cannot
 2. Easier to get donor kidney than heart.
- **BNP** very useful marker for monitoring heart damage in amyloid patients.
- **Serum free light chains** useful in monitoring amyloid, particularly when there is no other serum marker.

Step3: Interpretation

Consider:

- Is the band of paraprotein large or small? NB Size does not predict severity of disease.
 - Paraprotein size can be used to monitor an individual patient's disease.
- If this is a known patient, how is it progressing? Stable? Increasing?
- Is there secondary immune suppression of the other immunoglobulins?
- How old is the patient? Is it a surprising finding? Could it be an incidental finding?
- When should these results be repeated? Monthly/3 months/ 6 months/ annually.
 - May depend on condition and treatment. Rarely needs to be checked weekly, but may need daily if having plasmapheresis.



Immunofix identifying the bands in the CZE trace as IgG kappa and IgG lambda paraproteins.

4. Autoimmunity

Arises if the paraprotein (i.e. monoclonal immunoglobulin) has specificity for an autoantigen.

1. Anti-I, causing autoimmune haemolytic anaemia.
2. Anti-phospholipid, causing antiphospholipid syndrome
3. Rheumatoid factor (anti-Fc portion of IgG), may cause mixed cryoglobulinaemia (see Renal poster).
4. Anti-myelin associated glycoprotein (MAG), causing peripheral neuropathy.
5. Anti-C1 esterase inhibitor, causing acquired angioedema (see IMMUNODEFICIENCY poster).