Myeloma

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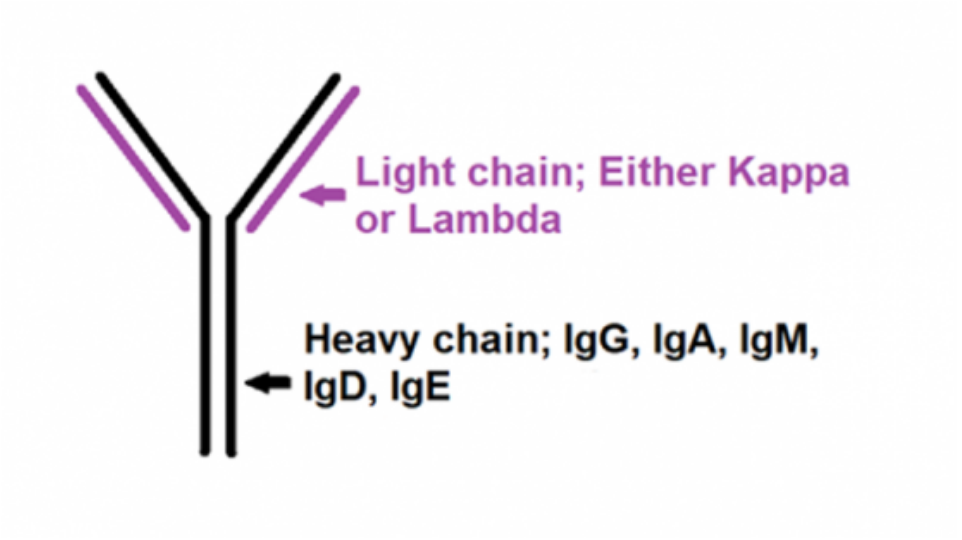
Author: Buku Medicine

People often get confused by the different tests for myeloma. Once you get a grasp of the terminology and importantly a tiny bit of the pathology (I promise there isn't much...) it makes a lot more sense.

What is myeloma?

Myeloma is a cancer of plasma cells. 'Normal' plasma cells are B cells that have been exposed to an antigen, and matured so that their primary function is to make immunoglobulin. Myeloma occurs when a plasma cell gains an oncogenic mutation leading to enhanced proliferation. These 'myeloma cells' proliferate and in almost all cases secrete a protein which is immunoglobulin-like, but performs no immune function.

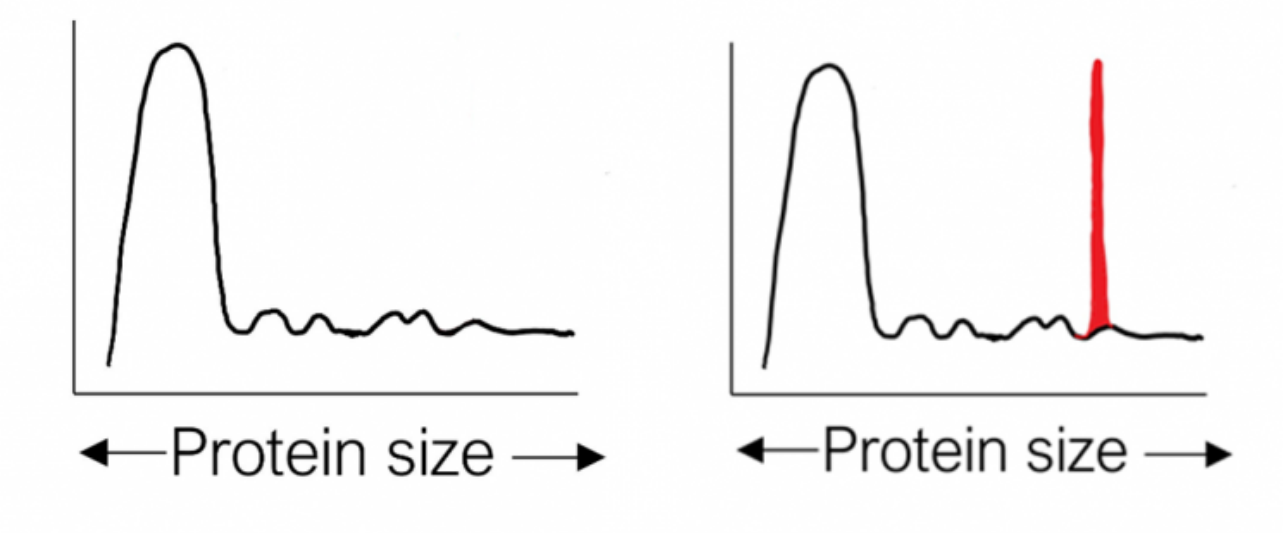
Going back to a little bit of physiology, immunoglobulin is made up of 2 elements; the heavy chain (e.g. IgG, IgA, IgM) and an associated light chain (kappa or lambda). For example IgG Kappa or IgA lambda.



This is important to help understand the tests that are performed for myeloma. Around 75% of myeloma cases produce a clonal protein with the heavy **and** light chains e.g. IgG kappa myeloma. This clonal 'whole' immunoglobulin-like protein is called a **paraprotein**. Around 20% of myeloma cases secrete **only a clonal light chain** e.g. lambda light chain myeloma. This is why we need to test for both heavy chains and light chains, otherwise we may miss 20% of myeloma cases if we only investigate for the heavy chains.

Tests

Serum electrophoresis (SEPHS) is the primary test for a paraprotein. SEPHS 'pulls' apart proteins by size. On the left is an amateur but educational sketch of a normal electrophoresis result, showing proteins spread along the plate by size from left to right. On the right is SEPHS showing a monoclonal 'spike'/'band'. This represents a paraprotein, and if detected, the lab will perform serum immunofixation which measures the type and amount of the paraprotein e.g. IgG kappa 13g/L.



For around 75% of patients this will be enough information for a diagnosis, but we must also test for light chains as 20% of myeloma cases only secrete light chains. The two ways to test for light chains are;

- **Serum free light chains (SFLC)** – This is a blood test which measures the amount of kappa and lambda light chains and calculates a ratio of one to the other. This should be within a 'normal' range as these are balanced in normal physiology. An increase in both is commonly seen in renal failure. A mild increase in one type may be seen in infection/inflammation. It is a very sensitive test, and very specific when results are significantly abnormal (as only plasma cell disorders like myeloma, MGUS or amyloidosis cause a **significant** imbalance in the kappa:lambda ratio). It can also be used to monitor response to treatment.
- **Urine Bence Jones protein** – This is a test for free light chains in the urine. It is not as sensitive, nor specific as it is only given as a positive or negative result, and light chains can be secreted into urine in infection/inflammation.

As you may have guessed, haematologists think the Bence Jones is a pretty poor test now we have SLFC, and that if SFLC is available this should be used first-line as it will 'miss' less cases of myeloma, and also cause fewer false positives.

Below is a flowchart to help put some of that information together;

Differential diagnosis

If either a paraprotein or clonal light chain (or both) are detected, this suggests a plasma cell disorder. Plasma cell disorders are monoclonal gammopathy of undetermined significance (MGUS), myeloma, amyloidosis or lymphoplasmacytic lymphoma (which deserves a whole blog to itself). All cases of

myeloma will have been preceded by MGUS, even if it was not known about beforehand (but not all MGUS cases will become myeloma - in fact very few will).

The difference between MGUS and myeloma is the number of plasma cells in the bone marrow (10% or more needed for diagnosis of myeloma) and importantly whether any end organ damage is present. MGUS is incredibly common, and the risk of transformation to myeloma is very low (1% per year). There are certain risk factors which make transformation more likely such as a paraprotein over 15g/L or an IgA paraprotein. A 'low risk' example-a 6g/L IgG kappa MGUS, with a normal serum free light chain (SFLC) ratio has only a 5% chance of transformation to myeloma at 20 years. A 17g/L IgA kappa MGUS with an abnormal SFLC ratio is higher risk, but still has a relatively low risk of transformation to myeloma of 58% at 20 years (I use a tool like https://qxmd.com/calculate/calculator_148/mgus-prognosis to risk stratify).

End organ damage is caused by two elements in the myeloma pathology;

- **The clonal myeloma cells**
    - **Anaemia** - As the myeloma cells expand they 'fill' the marrow reducing the space for haematopoiesis (erythropoiesis predominantly).
    - **Bony pain** – Myeloma cells increase osteoclast and reduce osteoblast activity leading to lytic bony lesions which cause pain and can cause pathological fractures.
    - **Hypercalcaemia** – As the myeloma cells cause bony destruction, calcium is released into blood.
- **Paraprotein or serum free light chains**
    - As these increase in volume, they cause renal tubular injury leading to renal failure which can present as acute kidney injury severe enough to need dialysis.
    - Hyperviscosity is much less common, and seen more with IgM paraproteins and presents with headache, visual disturbance, bleeding, or infarction including acute coronary syndrome or stroke.

Amyloidosis and lymphoplasmacytic lymphoma

A brief section about amyloidosis and then lymphoplasmacytic lymphoma.

- Amyloidosis sounds like something only Dr House would diagnose but again, like myeloma, understanding a bit of pathology helps significantly. Amyloidosis occurs when a plasma cell undergoes an oncogenic mutation, but instead of secreting only a paraprotein and light chains, it also secretes amyloid protein. This deposits in any tissue except the brain, but the commonest sites are the heart, nerves, and kidneys. Bony pain and hypercalcaemia are not seen. It is diagnosed with a biopsy of an affected tissue (this must be the aim rather than random gut biopsy/fat biopsy as the chance of a diagnosis is so much higher from affected tissue). It is treated with similar therapies to myeloma.
- Lymphoplasmacytic lymphoma (LPL) is a mouthful but again, makes sense with some pathology. This is a malignancy of B cells which has features of both myeloma (paraprotein secretion – almost always IgM) and lymphoma (sweats, fevers, weight loss, lymphadenopathy). Think of it as a cancer originating from a cell that has only partly matured from a normal B lymphocyte to plasma cell. **SO** if an IgM paraprotein is identified this will either be an IgM MGUS, or part of LPL – IgM myeloma is incredibly rare.

This table helps put together some of those test results with clinical features.

Condition	Paraprotein Or **Light chain**	Bone marrow plasma cells	End organ damage
MGUS	Under 30g/L **Kappa:Lambda ratio under 100**	<10%	No
'Smouldering' myeloma	Over 30g/L	10-60%	No

	Kappa:Lambda ratio under 100		
Myeloma	Does not always have to be significantly raised **Kappa:Lambda ratio usually over 100**	**≥10%**	**Yes (hyperCalcaemia, Renal impairment, Anaemia, Bony pain aka 'CRAB')**
Amyloidosis	Usually present **Ratio may be abnormal**	**Variable**	**Yes – heart failure, nephrotic syndrome, neuropathy (peripheral and autonomic)**
Lymphoplasmacytic lymphoma aka Waldenstrom's macroglobulinaemia	**IgM**	**Bone marrow usually performed but plasma cell % not diagnostic. Lymph node can also be used as biopsy source.**	**Lymphadenopathy, night sweats, fever and weight loss.**

We hope that this has been useful to break down some of the anxieties about myeloma and its tests. You can find more on the Buku Medicine app...

About the Buku Medicine App

Buku Medicine is a free App, available internationally, that I created (initially as Buku Haematology) with Prof Steve O'Brien from the Freeman Hospital, Newcastle, UK 3 years ago. I found as a junior haematology registrar that many questions we were asked could be avoided altogether with no need for specialist discussion with an easy to access resource like an App. This is the case for up to 21% of referrals to haematology. For those haematology queries that could not be avoided altogether, the App can recommend history/investigations for a further 60% of queries, and through that expedite patient care so the referrer can call the haematologist with the patient history and investigations fully prepped.

We have expanded the app over the last 3 years, and it is now installed on clinician devices in two North-East England NHS trusts, has the support of the regional haematology consultant body, is in the NHS App library and has over 13,000 active users.

In recent months we have also added renal and endocrine specialties to the app as their specialties are similar to haematology in the nature of many of the queries posed. We plan to add further modules in the coming months too.

The app can be downloaded from Apple and Google play AppStores, and if you like it please give us reviews on the AppStores to help promote our work.

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