Myeloma

1. Myeloma

Myeloma is tricky. Firstly, many of us find it a bit baffling: paraproteins, immunoglobulins, electrophoresis, light chains, monoclonal gammopathy….it's like a whole new language! Myeloma is also tricky because it's hard to spot. It has the distinction of being the cancer with the longest interval and largest number of consultations between first presentation and diagnosis: a third of cases take more than 12 months to diagnose.

Let's start with a reminder of what myeloma is and what it does to the body. That will help us understand (and remember) the symptoms which hopefully makes it easier to spot.

This article was reviewed and updated in July 2024.

1.1. What is myeloma?

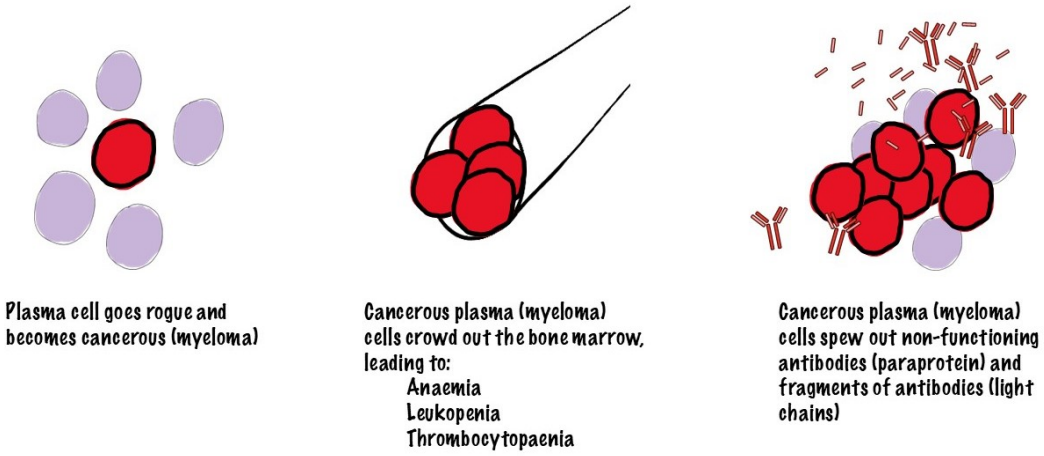
Myeloma is the third commonest haematological malignancy after leukaemia and lymphoma, but is still relatively rare. Most clinicians will diagnose only a handful of cases in their career.

Early diagnosis significantly improves survival. Advances in treatment improved median survival from 30 months before 2000 to 126 months between 2007 and 2016 (JAMA 2022;327:464). That's more than 10 years!

Myeloma and the blood

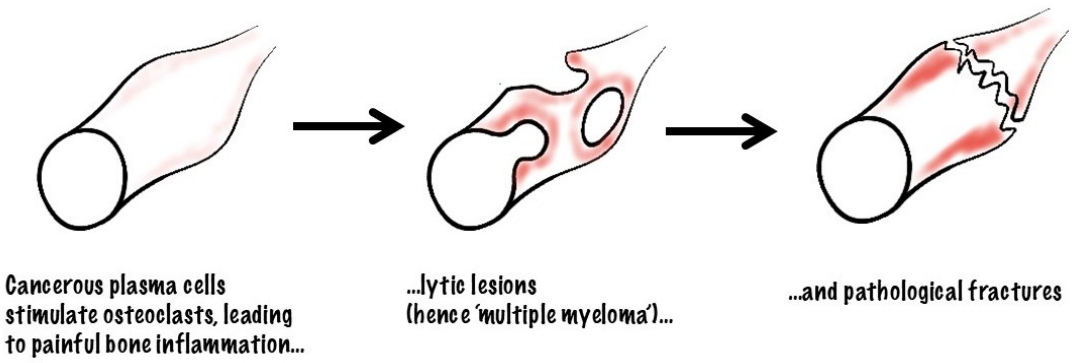
Myeloma is a cancer of plasma cells – white blood cells that produce antibodies, known as immunoglobulins. When large numbers of cancerous plasma cells are produced, they overtake the bone marrow and affect the production of all other cell lines, resulting in anaemia, leukopenia and thrombocytopenia.

The abnormal plasma cells may produce large amounts of abnormal immunoglobulin which is functionally impaired and inhibits production of normal immunoglobulin; the risk of infection may therefore also be increased. This abnormal immunoglobulin is known as paraprotein.



Myeloma and bones

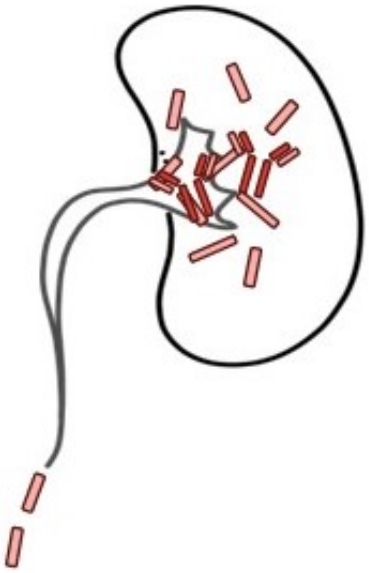
The cancerous plasma cells also have painful effects on the bones. They stimulate osteoclast activity, leading to bony inflammation, lytic lesions and, eventually, pathological fractures. This also causes raised calcium levels in the blood.



Myeloma and kidneys

Myeloma also frequently affects kidney function. Paraproteins and light chains clog up the kidneys, leading to reduced renal function and even kidney failure. When light chains pass through the kidney, they can be found in the urine as Bence Jones proteinuria. This was previously the gold

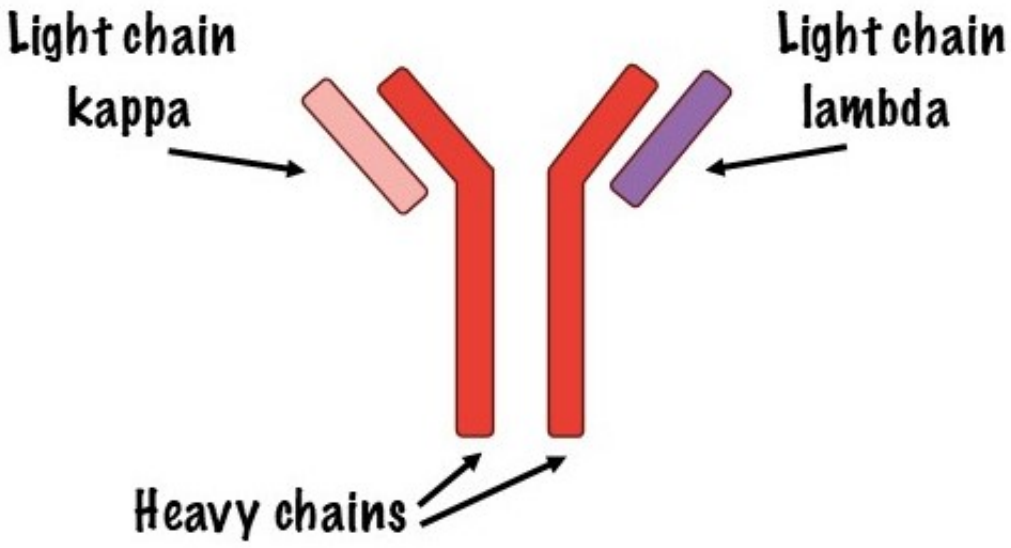
standard test for light chain myeloma. This has now been replaced by serum-free light-chain assay, which is a more sensitive test.



What are light chains?

Many of us find light chains a bit bewildering.

Cancerous plasma cells (myeloma cells) produce lots of a particular immunoglobulin, usually IgG, IgA or IgM (IgD and IgE are very rare and, if found, are always significant). The immunoglobulins produced are all exactly the same. They are clones of the original cancerous plasma cell. We call this a monoclonal gammopathy, and it can be picked up on electrophoresis as a monoclonal band. Immunoglobulins are composed of heavy chains and light chains. 15% of myelomas only produce one of the light chains, hence the importance of testing for light chains. The light chains are called kappa and lambda, and a myeloma that produces lots of one of the light chains shows up as a skewed ratio of kappa to lambda on a serum-free light-chain assay. You may have seen this on lab reports.



What about Bence Jones proteins?

Historically, we used to check for light chains by looking for Bence Jones proteins *(another name for light chains)* in the urine, but now NICE guidance recommends that we use serum-free light-chain assay instead if this is available in your area. On occasion, we may be asked to do urine Bence Jones proteins if the person with myeloma is part of a clinical trial (British Journal of Haematology 2021;193(2):205).

1.2. Myeloma presentation

Given the effect of myeloma cells in the body, we can see why the most common presenting symptoms are (BMJ 2012;344:d79530):

- Bone pain, particularly back and rib pain.
- Fatigue.
- Breathlessness.
- Weight loss.

1.3. NICE guidance on myeloma

NICE makes the following recommendations about investigation and referral for myeloma (NICE 2015, NG12).

Offer FBC, serum calcium and ESR (or plasma viscosity) if ≥60y and:

- Persistent bone pain (particularly back pain) OR
- Unexplained fracture.

If ≥60y with hypercalcaemia or leukopenia, and presentation is consistent with possible myeloma:

- OFFER very urgent (within 48h) serum protein electrophoresis and serum-free light-chain assay (or Bence Jones protein urine test if serum-free light-chain assay is not available in your area).

At any age, if raised ESR (or plasma viscosity) and presentation is consistent with possible myeloma:

- CONSIDER very urgent (within 48h) serum protein electrophoresis and serum-free light-chain assay (or Bence Jones protein urine test if serum-free light-chain is not available in your area).

Refer via the suspected cancer pathway if serum protein electrophoresis or light-chain ratio suggest myeloma.

Myeloma UK's diagnostic tool for primary care gives some useful guidance on interpretation of test results.

Interpreting results (some labs may have slightly different reference ranges)

Abnormal result	Action
Any paraprotein/abnormal light-chain ratio **PLUS** symptoms suggesting **urgent problem, e.g. cord compression, AKI.**	Immediate referral to haematology (or other pathway dictated by presentation, e.g. cord compression).
Moderate paraprotein: • IgG >15g/L. • IgA or IgM >10g/L.	Refer via suspected cancer pathway.
Abnormal light-chain ratio: • <0.1 or >7 or Bence Jones proteinuria.	
Any IgD or IgE paraprotein.	

From: Myeloma Diagnostic Tool: guidance for GPs (Myeloma UK, 2022), accessed November 2023.

However, if we follow these guidelines alone, we will miss cases – so let's explore further.

1.4. Myeloma is easily missed

One-third of myelomas are diagnosed as emergency presentations (BJGP 2022;72(723):462).

Why?

More than 70% of cases of myeloma occur in over-65-year-olds, and it presents with relatively vague symptoms.

The *individual symptoms* of myeloma, including back pain, fatigue and breathlessness, are seen commonly in primary care. **Even in combination,** these symptoms have a PPV for myeloma of <1%.

This contributes to delay, both before and after presenting to primary care.

What does this mean in practice?

We need a high degree of suspicion **and** need to order appropriate blood tests to increase our chances of earlier detection.

The solution *(sort of!)*: combining symptoms with blood results can significantly improve the pick-up rate for myeloma.

A case–control study used the CPRD to identify and quantify the risk of myeloma using combinations of specific clinical features with abnormal blood results (BJGP 2015; 65(631):e106):

Symptom COMBINATIONS		**PPV (chance of the person having myeloma)**
Hypercalcemia AND	Back pain (2nd episode)	>10%
	Fracture	>10%
	Joint pain	>10%
	Rib pain	>10%

	Back pain (1st episode)	4.0%
	Chest infection	2.0%
	Chest pain	1.9%
	SOB	1.5%
	Combined bone pain	1.4%
Leukopenia AND	Nosebleeds	>10%
	Fractures	>10%
	Combined bone pain	>5%
	Back pain (2nd episode)	2.0%
Raised inflammatory markers AND	Back pain (2nd episode)	1.1%

Based on this study (and in addition to NICE, detailed earlier), the authors suggest that we should:

- Offer **FBC** and **ESR** to any patient aged ≥60y presenting with bone pain, weight loss or nosebleeds, or with a second episode of back pain. If these tests are abnormal, move on to second-line tests.
- They also state that a normal calcium does not rule out myeloma (it rises late) so, if it IS raised, it definitely needs further investigation.

For simplicity, we think this means: if you suspect myeloma, check FBC + ESR + calcium; if any are abnormal, do second-line tests to look for paraprotein and light chains.

1.5. Which blood tests?

The vague nature of the presenting symptoms means that we are likely to be considering several diagnoses.

The same authors as the above research used the CPRD to do a case–control study looking at which blood tests are most helpful in primary care (BJGP 2018; DOI:https://doi.org/10.3399/bjgp18X698357). They concluded:

- **If FBC and ESR (or plasma viscosity) are normal, myeloma is very unlikely.** This performs sufficiently well as a 'rule-out' screen in primary care. This is because haemoglobin starts to fall 2–3 years prior to a myeloma diagnosis.
- If ESR/plasma viscosity is raised in a symptomatic patient, we should do a calcium and serum protein electrophoresis (including immunoglobulins and light chains).
- Don't be reassured by a normal CRP. CRP is often normal in people with myeloma, with no difference between cases and controls in this study.
- Don't be reassured by a normal serum calcium or creatinine. These rise later in the disease. If normal, this does not rule out myeloma.
- No SINGLE blood test can rule out myeloma.

1.6. Myeloma blood tests: a two-step process

First-line blood tests

Here, we are looking for abnormal bloods that may suggest myeloma (FBC + ESR + calcium), but we are also considering a wider 'vague presentation differential'. Pragmatically, we might request:

Blood test	What are we looking for?
FBC	Anaemia, leukopenia.
ESR and/or plasma viscosity	Raised levels increase the likelihood of myeloma.
CRP	May be normal in myeloma. If raised, consider other possibilities as well.
Calcium	Often raised, but less sensitive/specific than ESR/plasma viscosity and Hb.
U&E/LFTs	End-organ damage.
PSA	May be appropriate in male patients presenting with bone pain.

Second-line blood tests to look for paraprotein

- Request serum protein electrophoresis and serum-free light-chain assay (or urinary Bence Jones proteins if serum-free light-chain assay is not available in your area) if ESR/plasma viscosity, FBC or calcium are abnormal, or if creatinine is rising without explanation.

This might surprise some of us. It might seem odd not to do serum electrophoresis at the same time as the first-line bloods. And, of course, we CAN do this if we are highly suspicious of myeloma. But because no symptoms or signs perform that well, AND a normal ESR and normal FBC perform well enough as a rule-out screen in primary care, a two-step approach is reasonable for most.

1.7. How good are plain X-rays for lytic lesions?

- Plain X-rays only show lytic lesions when 30–50% of the bone cortex is eroded.
- CT and PET scans are much more sensitive, but are not available to us in primary care.
- We should beware of false negative X-rays when investigating bone pain, and seek advice and guidance if clinical uncertainty remains (JAMA 2022;327(5):464-477).

1.8. Could a risk-prediction tool help?

Maybe…

A UK-based retrospective cohort study (using the CPRD) developed and tested two clinical prediction tools which could automatically look at symptoms (nosebleeds; back, rib or chest pain), blood results, age and sex, and flag the possibility of myeloma in cases where it had otherwise not been considered (BJGP 2021;71:e347).

The prediction tools had reasonable sensitivity and specificity. But here is the problem: the tools rely on accurate clinical coding and, as myeloma prevalence is so low, a GP would have to test over 250 patients to discover

one extra cancer.

That's a LOT of extra pop-up-prompted healthcare activity; this tool would need to be implemented into our practice-based systems. So, we think this is a 'watch this space'.

1.9. Management

In primary care, all myeloma patients should be offered annual influenza immunisation and be considered for pneumococcal vaccination, regardless of age.

The rest of myeloma management is really a secondary care issue and was covered by a NICE guideline (NG35 updated 2018).

For those who are interested:

- People with myeloma are divided into those who are eligible for autologous stem cell transplantation and those who are not.
- Chemotherapy is the mainstay of treatment, either in preparation for stem cell transplant (with the aim of cure) or to achieve a clinical remission where there is no evidence of end-organ damage and no detectable paraprotein.
- All patients with myeloma are offered bisphosphonates to reduce the risk of pathological fractures and skeletal damage. These are given intravenously in secondary care, but we should be aware that these patients are at risk of complications, including renal impairment and osteonecrosis of the jaw.

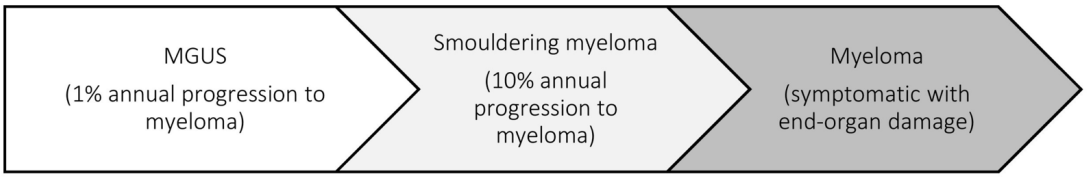
Complications of treatment

NICE (NG35 updated 2018) highlights some of the common complications of treatment for myeloma. This is where we might be called by patients, and it is useful to have a simple overview:

- Peripheral neuropathy can be a side-effect of chemotherapy treatment.
- Thrombosis: patients may be offered thromboprophylaxis. If a thrombotic event is suspected, refer as normal.
- Fatigue: check for anaemia. Haematology may consider erythropoietin infusions to maintain haemoglobin between 110 and 120g/L.
- Infection due to therapy-related neutropenia. Some will be on antiviral prophylaxis (JAMA 2022;327(5):464-477).

1.10. Smouldering myeloma and monoclonal gammopathy of uncertain significance (MGUS)

These two conditions are precursors of myeloma and fall on a spectrum along the way to active myeloma. Both have the potential to become myeloma and are likely to require monitoring:



Monoclonal gammopathy of undetermined significance (MGUS)

- 3–5% of people over 65y and 10% of those over 80y have MGUS. An

estimated 1% each year progress to multiple myeloma or other lymphoproliferative disease (JAMA 2022;327(5):464-477). Most will never develop myeloma.

- These people are picked up while asymptomatic (perhaps through blood tests for other conditions). They do not have symptoms of myeloma or any end-organ damage.
- They may have a mildly raised paraprotein level or a mildly abnormal light-chain ratio NOT reaching the threshold for a suspected cancer referral.

Smouldering myeloma

- This is the presence of significant paraprotein but with no evidence of end-organ damage.
- It is an intermediate stage between MGUS and myeloma.
- 10% of people with smouldering myeloma will progress to myeloma each year (JAMA 2022;327(5):464-477).

Interpretation of blood test results

Abnormal result	Action
Minor concentration of paraprotein WITHOUT relevant symptoms: • IgG <15g/L. • IgA or IgM <10g/L.	*Common in the elderly.* • Recheck in 2–3m to confirm pattern and assess for progression. • If paraprotein concentration increases (25% and >5g/L) or patient develop symptoms: urgent referral.
Minor abnormal serum-free light-chain ratio (>0.1 and <7, but outside normal range).	

From: Myeloma Diagnostic Tool: guidance for GPs (Myeloma UK, 2022), accessed November 2023.

If results are not clear, you have ongoing concerns or there is a persistent mild abnormality, we suggest seeking advice and guidance from haematology.

Management

Monoclonal gammopathy of undetermined significance (MGUS)

Management usually involves active surveillance with serum immunoglobulins/serum-free light-chain ratio; the hospital usually recommends the appropriate interval (or follows up directly). Some areas have a shared care arrangement for monitoring.

- In secondary care, if their bone marrow biopsy has less than 10% plasma cells, or if their serum monoclonal protein is raised but less than

30g/L, they are given a diagnosis of MGUS.

Smouldering myeloma

NICE (NG35 updated 2018) recommends 3-monthly monitoring for the first 5y after diagnosis, and then a personalised plan based on individual risk factors for progression.

Monitoring should include:

- Assessment of symptoms.
- FBC, renal function, bone profile, serum immunoglobulins and electrophoresis.
- Serum-free light-chain assay (if appropriate).

Routine skeletal surveys are not recommended; instead, imaging should be requested according to new bone symptoms.

Myeloma

- Rare and easily missed.
- Consider it in those ≥60y with bone pain and back pain, fatigue, breathlessness and weight loss.
- No individual or grouped symptoms have strong PPVs of >1%!
- Think myeloma? Think FBC + ESR (or viscosity) + calcium blood tests.
- If ANY of these are abnormal, do second-line tests to look for paraprotein: serum protein electrophoresis with serum-free light-chain assay (or, if serum-free light-chain assay is not available, urine Bence Jones proteins).
- A normal FBC AND ESR is good enough to rule out myeloma in primary care.
- Normal calcium alone does not rule out myeloma (calcium and creatinine tend to rise later).
- Normal plain X-ray does not rule out myeloma.
- Be aware of smouldering myeloma and MGUS – we might be asked to follow-up.

Useful resources:

Websites (all resources are hyperlinked for ease of use in Red Whale Knowledge)

- UKONS support tool (this is a guide to potential side-effects of oncology treatments and how to initially advise/manage them)

Useful resources for patients:

Websites

- Macmillan Cancer Support – myeloma

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