MyelomaUK

Myeloma and MGUS

A Guide for GPs

Disclaimer

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1. Introduction

This guide is written for General Practitioners (GPs) to help in the diagnosis of myeloma and monoclonal gammopathies. It focuses on the tests that can be requested in primary care, how to interpret these test results, and guidance on referral.

About myeloma

- Myeloma is a blood cancer that arises in the plasma cells of the bone marrow
- On average 5,800 people are diagnosed with myeloma every year in the UK
- 74% of myeloma diagnoses are in people aged over 65, but it affects younger people too
- Myeloma is 2–3 times more common in Black people compared with White and Asian people
- Complications of myeloma include bone damage, anaemia, infections, and renal impairment
- Diagnosis after GP referral has a better survival than after diagnosis via emergency routes

2. What is myeloma, smouldering myeloma and MGUS?

Myeloma is a blood cancer that arises in the plasma cells of the bone marrow. Genetic alterations can lead to uncontrolled proliferation of these plasma cells and the secretion of high levels of abnormal and non-functional immunoglobulins (paraproteins). These changes can lead to complications including bone damage, anaemia, infections, and renal impairment.

Myeloma is classified according to the type of defective immunoglobulin (Ig) that is produced by the plasma cell clone. A single Y-shaped immunoglobulin consists of two identical heavy chains (type G, A, D, E or M) and two identical light chains (kappa or lambda). Light chains in the urine are commonly known as Bence Jones proteins (BJP). The majority of patients have IgG type myeloma. IgA is the next most common, with IgM, IgD and IgE types all rare.

Around 20% of patients have light chain myeloma, where the myeloma cells produce only light chains and no whole immunoglobulins. As only one type of light chain is produced, an abnormal serum free light chain (sFLC) kappa:lambda ratio indicates this type of myeloma, as well as high absolute levels of either kappa or lambda light chains. Light chain myeloma is particularly damaging to the kidneys as the light chains can accumulate and block the renal tubules.

Around 1–2% of myeloma cases are non-secretory, meaning that no measurable paraprotein is detected at all.

The current UK working definition of active myeloma comes from the International Myeloma Working Group (IMWG),[1] which lists myeloma-defining events (MDEs) as part of the diagnostic criteria, as noted in Table 1. These criteria include **CRAB** features (hyper**C**alcaemia, **R**enal, **A**naemia, **B**one), and three additional MDEs, known as **SLiM** criteria. This combination assists haematologists to diagnose myeloma sooner and start treatment earlier.

Table 1. Diagnostic criteria for active myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and one or more of the following **myeloma-defining events:**

Hyper**C**alcaemia: >2.75 mmol/L serum calcium or >0.25 mmol/L higher than the upper limit of normal

Renal insufficiency: serum creatinine >177 µmol/L or creatinine clearance <40 ml/min

Anaemia: haemoglobin <100 g/L or >20 g/L below lower limit of normal

Bone lesions: ≥1 osteolytic lesion on X-ray, CT or PET/CT (>5 mm in size)

- **S**ixty percent or greater (≥60%) clonal plasma cells in bone marrow
- Ratio of abnormal **Li**ght chains/normal light chains ≥100, provided the involved light chain is >100 mg/L
- >1 focal lesion on **M**RI (>5 mm in size)

Patients with active myeloma will, at some stage, have passed through two earlier phases of disease, monoclonal gammopathy of undetermined significance (MGUS) and smouldering myeloma as defined in Table 2.

Table 2. Definition of MGUS and smouldering myeloma

MGUS

- Pre-malignant
- <30 g/L serum paraprotein
- <10% clonal plasma cells
- No myeloma-defining events

Smouldering myeloma

- Malignant
- Early form of myeloma (usually progresses over time)
- ≥30 g/L serum paraprotein
- 10–60% clonal plasma cells
- No myeloma-defining events

In both MGUS and smouldering myeloma, a monoclonal protein (paraprotein) is present and there is evidence of proliferation of clonal plasma cells in the bone marrow, but patients usually show no symptoms. MGUS and smouldering myeloma are often picked up as an incidental finding, with a paraprotein being detected on routine blood tests.

Patients with active myeloma need to start treatment straight away to halt the disease process and stop further end organ damage. Those with smouldering myeloma are monitored regularly for signs of progression to active myeloma. The risk of progression from smouldering to active myeloma is summarised in Table 3.[2]

Table 3. Risk of progression from smouldering to active myeloma

Period after diagnosis	Approximate risk of progression to active myeloma during this period
0–5 years	50%
5–10 years	15%
10–20 years	10%

3.
The importance of early diagnosis

Primary care clinicians play a critical role in the early diagnosis of myeloma by being able to:

- Accurately test and refer patients presenting with symptoms of suspected myeloma
- Manage patients with low-risk MGUS, knowing when to seek advice or make a referral to haematology

Evidence shows that myeloma patients experience some of the longest delays to diagnosis of all cancer patients, and this remains the case despite national referral guidelines for suspected cancer.[3, 4] This is in part due to the vague and non-specific nature of symptoms.

A myeloma patient's route to diagnosis has an impact on survival. Diagnosis after presentation via GP referral has a better one-year survival than via an emergency presentation (88% vs 62%, respectively).[5] Furthermore, 25% of myeloma patients who present as an emergency die within the first six months of diagnosis compared to <10% of those presenting via other routes.[6]

Patients presenting as emergencies often do so with acute and/or late-stage complications such as fractures, severe infections, acute renal failure, and spinal cord compression, with associated effects on function and quality of life. A study of cancer patients that presented as an emergency, found that, of 18 different cancer types, myeloma patients were the most likely to have had three or more prior GP consultations.[7]

Raising awareness of the typical signs and symptoms of myeloma may help GPs, and other healthcare professionals who first encounter potential myeloma patients, to suspect and investigate this cancer earlier and reduce the likelihood of emergency presentation.

4. Red flags of myeloma

Myeloma is often characterised by vague, non-specific symptoms that may be attributed to comorbidities or considered too non-specific to suggest cancer. It is critical to consider myeloma, however, when such symptoms arise, particularly in combination.

There are several red flag symptoms that should lead to a suspicion of myeloma:

- Persistent or unexplained pain (>4–6 weeks, presenting as generalised or localised), particularly in the back or ribs
- Spontaneous fractures, including osteoporotic vertebral fractures
- Hypercalcaemia; reduction in renal function
- Recurrent or persistent infections
- Unexplained anaemia
- Nosebleeds or unexplained bleeding
- Unexplained breathlessness
- Generally unwell – fatigue, weight loss, suspicion of underlying cancer
- Unexplained peripheral neuropathy

It is critical to consider myeloma when such symptoms arise, particularly in combination. The following have a positive predictive value (PPV) >10 for myeloma.[8]

- **Hypercalcaemia**, plus any of the following:
  - two episodes of back pain
  - fracture; joint pain
  - rib pain
- **Leukopenia**, plus either of the following:
  - nosebleeds
  - fractures

As with many other cancers, a GP's underlying suspicion of cancer can be an important and powerful indicator to take further investigative tests.

5. Requesting tests

Some GPs have the option to request a 'myeloma screen' while others need to request the combination of individual tests, listed below:

- Full blood count
- Adjusted/corrected serum calcium
- Serum creatinine
- Plasma viscosity or ESR*
- Serum protein electrophoresis (to check for a paraprotein)
- sFLC assay (or urine BJP if sFLC is unavailable)**
- Serum immunoglobulins (IgG, IgA, and IgM)

* as recommended by the National Institute for Health and Care Excellence (NICE)[3]

** testing for serum or urinary light chains, as well as serum protein electrophoresis, is important because 20% of myeloma cases may be light chain only.

6. Interpreting test results

The critical hallmark of a monoclonal gammopathy is evidence of a monoclonal band on electrophoresis (paraprotein) or monoclonal excess of light chains in serum or urine. An abnormal serum protein electrophoresis and/or abnormal sFLC ratio will pick up ~98% of myeloma patients.[9] Serum free light chain assay is not available to all GPs and so urinary BJP may be requested instead. Note: the latter is not as sensitive and some cases of light chain myeloma may not be detected.

If a monoclonal band is present, most laboratories will automatically perform immunofixation to define the Ig class (IgG, IgA and rarely IgM, D or E) and light chain type (kappa or lambda). Defining the Ig class early can help direct future investigations.

Serum immunoglobulins are typically reduced in myeloma (immunoparesis), except for the affected Ig type. Typical normal values for each of the tests covered above are summarised in Table 4.

Table 4. Typical normal ranges of myeloma screen blood tests

Blood test	Testing for	Normal range
Full blood count	Haemoglobin (men)	135–180 g/L
	Haemoglobin (women)	115–160 g/L
Serum Ig and protein electrophoresis	Paraprotein	0 g/L
Urea, electrolyte and creatinine	Urea	2.5–6.7 mmol/L
	Creatinine	70–150 µmol/L
	Calcium	2.12–2.6 µmol/L
sFLC assay	Kappa light chain (κ)	3.3–19.4 mg/L
	Lamda light chain (λ)	5.71–26.3 mg/L
	sFLC ratio (κ/λ)	0.26–1.65

7. Looking for trends and safety netting

In addition to new onset symptoms, underlying trends and combinations of blood test results may be helpful to consider. Such as:

- Falling haemoglobin levels and rising erythrocyte sedimentation rate (ESR) can occur in the two years prior to a myeloma diagnosis[10, 11, 12]
- The combination of normal haemoglobin, plus normal ESR or plasma viscosity (PV) can help rule out myeloma.[11]
- An increase in attendance by patients who rarely visit their GP, particularly for non-specific, vague and ongoing symptoms. For example, continuing and/or unexplained pain, presenting as generalised or localised, particularly in the back or ribs. Also recurring/persistent infections.
- Increasing pain in patients with chronic conditions such as arthritis, particularly if their usual analgesia has become less effective

The following general safety netting measures are important in myeloma, where symptoms can be non-specific in nature:

- Following up patients until their symptoms are explained, resolved or they are referred for further investigations
- Booking a follow-up appointment with the patient to discuss results of investigations
- Ensuring that patients know when to come back if symptoms do not resolve, and to reconsult if things change
- Checking patients' understanding of follow-up advice and that they are clear about what symptoms to look out for and report

8. When to refer

Referral needs to be in line with relevant national referral guidelines for cancer, which include both NICE guidance and Scottish government referral guidelines for suspected cancer.[3, 13]

Immediate or emergency referral is needed for any patient showing signs of acute kidney injury, significant hypercalcaemia or spinal cord compression as these clinical situations are emergencies.

Urgent referral to haematology on a suspected cancer referral pathway is needed for patients with one or more of the following:

- A new IgG paraprotein >15 g/L
- A new IgM or IgA paraprotein >10 g/L
- Identification of an IgD or IgE paraprotein (regardless of concentration)
- A significantly abnormal sFLC ratio (<0.1 or >7) or identification of BJP
- Any serum paraprotein <10 g/L but where there is clinical suspicion of myeloma
- Imaging confirming a lytic bone lesion or abnormality suspicious of myeloma
- Symptoms suggestive of underlying myeloma

Non-urgent/routine referral or discussion with clinical haematology may be appropriate for patients with a low level paraprotein or mildly abnormal sFLC ratio and no symptoms suggestive of myeloma. However, rechecking the serum or urine in 2–3 months is recommended to monitor the disease pattern and assess progression. Patients whose paraprotein concentration increases by >25% and >5 g/L or who develop symptoms will need an urgent referral to haematology as described above.

Response to results and referral pathway recommendations are summarised in Table 5. This table forms part of the Myeloma UK GP Myeloma Diagnostic Tool.[14]

Table 5. Response to results & referral guidance

• Any paraprotein/abnormal sFLC ratio **with** significant symptoms indicative of an urgent problem (e.g. spinal cord compression, acute kidney injury)	Recommend **immediate referral** to Clinical Haematology
• Moderate concentration of paraprotein (IgG > 15 g/L, IgA or IgM > 10 g/L) • Identification of an IgD or IgE paraprotein (regardless of concentration) • Significant abnormal sFLC ratio (< 0.1 or > 7) ◦ Identification of BJP	Recommend **urgent referral** to Clinical Haematology (2-week rule)
• Minor concentration of paraprotein (IgG < 15 g/L, IgA or IgM < 10 g/L) **without** relevant symptoms • Minor abnormal sFLC ratio (> 0.1 and < 7, but outside normal range) This pattern is common in elderly patients	Recommend **recheck** serum and urine in 2–3 months to confirm pattern and assess any progression. Patients whose paraprotein concentration increases (25% and > 5 g/L) or develop symptoms will need an **urgent referral**. **Discuss** with your Clinical Haematology Department if results not clear or concerns.
• No serum paraprotein • Normal sFLC ratio (0.26–1.65)* ◦ No BJP • Normal immunoglobulin levels *some laboratories may have a slightly different reference range	Myeloma very **unlikely** but symptoms may still need to be investigated with other clinical specialties

9. Managing MGUS in primary care

Patients with a diagnosis of MGUS require regular monitoring for signs of progression to myeloma or other associated disorders. The risk of progression from MGUS to myeloma is 1% per year and is dependent on a number of factors including:

- Type of paraprotein: IgA and IgM are associated with a higher risk of progression
- Higher levels of paraprotein
- Abnormal sFLC ratio

The most widely used risk stratification model for progression is summarised in Table 6 and can help guide the management and follow-up of MGUS patients.

Models of follow up

MGUS patients may be followed up by primary care, the hospital, or a combination of the two. Protocols and local commissioning can vary. For example, some low-risk MGUS patients are managed exclusively in primary care and referred only to secondary care if there are signs of progression. Others are managed solely in secondary care.

MGUS monitoring combines blood tests and checking for symptoms. Patients are referred to haematology if any of the following happen:

- Increased paraprotein concentration of >25% (a minimum absolute increase of 5 g/L)
- Symptoms indicative of myeloma occur
- Unexplained anaemia, reduced renal function or hypercalcaemia occur

Table 6. Risk stratification model for progression from MGUS to myeloma[15]

Risk group (score)*	Risk of progression at 20 years (%)
Low (0)	5
Low-intermediate (1)	21
High-intermediate (2)	37
High (3)	58

* score 1 for each of the following:
  - Serum paraprotein >15 g/L
  - Non-IgG subtype
  - Abnormal sFLC ratio (<0.26 or >1.65)

Current guidance suggests checks every 3–4 months in the first year, followed by 6–12 month monitoring thereafter.[16]

Information and reassurance are vitally important in helping manage the feelings of anxiety and uncertainty that patients experience when diagnosed with a pre-malignant condition such as MGUS. It is important that patients understand the symptoms to look out for and report, should they occur. Myeloma UK provides an information sheet on MGUS, which includes symptom awareness and living with an MGUS diagnosis.

Associated disorders

Monoclonal gammopathy can be associated with other systemic disorders in absence of true progression to myeloma. These conditions are termed monoclonal gammopathy of clinical significance (MGCS). Although the gammopathy is benign, there may be symptoms and complications that require early intervention. These conditions include:

- AL amyloidosis
- Light chain deposition disease
- A variety of renal syndromes termed monoclonal gammopathy of renal significance (MGRS)
- POEMS syndrome (**P**eripheral neuropathy, **O**rganomegaly, **E**ndocrinopathy, **M** protein, **S**kin changes).

The typical organs affected are heart, kidneys, nerves and skin. A patient with MGUS developing unexplained heart failure, renal impairment (especially with proteinuria or haematuria), progressive peripheral neuropathy or autonomic neuropathy requires referral for further investigations of MGCS. Unexplained inflammatory and skin disorders may also be MGCS syndromes. All MGUS patients should have measurement of NT-proBNP and urine dip stick for proteinuria during routine follow up, to help in the early detection of an MGCS syndrome.

10. Managing patients with myeloma in primary care

Patients with active and smouldering myeloma are managed by a haematologist but will still be seen in primary care for management of other conditions, depending on their needs.

Myeloma treatment consists of a combination of drugs; typically, this will be chemotherapy, steroids and treatments such as proteasome inhibitors and/or immunomodulatory drugs. Younger, fitter patients are usually offered an autologous stem cell transplant after initial chemotherapy. Myeloma treatment has a variety of side effects, which are monitored by the haematology team, and may be evident if the patient is seen in primary care.

As a relapsing remitting disease, myeloma patients will typically have periods of time on treatment, but also periods in remission or with stable disease. The onset of new symptoms and potential myeloma progression should always be a consideration during GP appointments.

Points to be aware of when seeing myeloma patients include:

- ☐ Increased risk of venous thromboembolic events, particularly when patients are receiving myeloma treatment with chemotherapy and steroids
- ☐ Side effects of high-dose steroids, including the risk of diabetes, or changes in a patient's existing diabetes management while on steroids
- ☐ Risk of neutropenic sepsis if on chemotherapy or following stem cell transplant
- ☐ Ongoing susceptibility to infections and a reduced threshold for using antibiotics
- ☐ Need for vaccinations – myeloma patients are recommended to have the seasonal influenza vaccine annually, and the pneumococcal vaccine every five years. Repeat childhood vaccines may also be advised following stem cell transplantation, depending on local policy. COVID-19 vaccination is required in line with the relevant government guidance.
- ☐ Chronic myeloma symptom management, including pain, neuropathy and fatigue
- ☐ Avoidance of non-steroidal anti-inflammatory drugs (NSAIDs), which can worsen renal function
- ☐ Psychosocial effects of diagnosis and treatment, and the need for patient and carer support

11. References

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2. Kyle et al. (2007) Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med, 356(25): 2582–90
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13. Scottish Government: Scottish referral guidelines for suspected cancer. https://www.gov.scot/publications/scottish-referral-guidelines-suspected-cancer-january-2019

14. Myeloma UK GP Myeloma Diagnostic Tool. https://academy.myeloma.org.uk/resources/gp-myeloma-diagnostic-tool

15. Rajkumar (2005) MGUS and smoldering multiple myeloma: update on pathogenesis, natural history, and management. Hematology Am Soc Hematol Educ Program, 340–5

16. Bird et al. (2009) UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). Br J Haematol, 147(1): 22–42

12. Further information

Educational Resources

- Myeloma UK resources for GPs and other healthcare professionals are available at academy.myeloma.org.uk These include:
  - GP Diagnostic Tool
  - Myeloma Diagnosis Pathway
  - Macmillan Ten Top Tips
- Primary care educational modules:
  - Gateway C Myeloma course https://www.gatewayc.org.uk/courses
  - BMJ Myeloma Module https://new-learning.bmj.com/course/10066091
- Cancer Research UK myeloma statistics https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma
- Haematological Malignancy Research Network (HMRN) myeloma factsheets https://hmrn.org/factsheets#myeloma

Guidelines

- NICE guideline [NG12] suspected cancer: recognition and referral
  https://www.nice.org.uk/guidance/ng12

- NICE guideline [NG35] Myeloma: diagnosis and management
  https://www.nice.org.uk/guidance/ng35

- Scottish Government: Scottish referral guidelines for suspected cancer
  https://www.gov.scot/publications/scottish-referral-guidelines-suspected-cancer-january-2019

- British Society for Haematology (BSH) and UK Myeloma Forum (UKMF) guidelines on the diagnosis, investigation and initial treatment of myeloma
  https://b-s-h.org.uk/guidelines/guidelines/guidelines-on-the-diagnosis-investigation-and-initial-treatment-of-myeloma

- BSH guidelines for the use of imaging in the managment of patients with myeloma
  https://b-s-h.org.uk/guidelines/guidelines/use-of-imaging-in-the-management-of-patients-with-myeloma

- BSH and UKMF guidelines for screening and management of late and long-term consequences of myeloma and its treatment
  https://b-s-h.org.uk/guidelines/guidelines/screening-and-management-of-late-and-long-term-consequences-of-myeloma-and-its-treatment

Patient information

- Tests and investigations in myeloma Infoguide
  https://myeloma.org.uk/documents/tests-and-investigations-in-myeloma-infoguide

- MGUS Infosheet
  https://myeloma.org.uk/documents/monoclonal-gammopathy-of-undetermined-significance-mgus-infosheet

- MGUS Diary
  https://myeloma.org.uk/mgusdiary

- Infopack for newly diagnosed myeloma patients
  https://myeloma.org.uk/documents/infopack-for-newly-diagnosed-patients

- Smouldering myeloma Infosheet
  https://myeloma.org.uk/documents/smouldering-myeloma-infosheet

The full list of our publications for patients can be found at myeloma.org.uk/publications

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MyelomaUK

Myeloma UK is the only organisation in the UK dealing exclusively with the incurable blood cancer myeloma and related conditions.

We deliver better patient outcomes through our dedicated programmes covering early diagnosis, research, treatment access, healthcare services improvement, and patient information and support.

For any queries or additional resources for healthcare professionals on myeloma and unrelated conditions:

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