12. PARAPROTEINS (MGUS)

12.1 SCOPE

Several disorders are associated with the presence of a monoclonal protein in the blood (paraprotein and/or abnormal serum free light chain ratio) or urine (Bence Jones protein). These include MGUS (monoclonal gammopathy of undetermined significance), myeloma, lymphoma, chronic lymphocytic leukaemia (CLL) and AL amyloidosis.

MGUS is defined by a low level of monoclonal protein and the absence of any symptoms/signs attributable to a plasma cell disorder or lymphoma. It is asymptomatic and very common, found in 3-5% of people aged over 70 years and up to 10% in people aged over 80 years.

MGUS does not require treatment but there is a potential to progress to symptomatic disease. Patients with intermediate-risk or high-risk MGUS therefore need long term monitoring.

12.2 ASSESSMENT

MGUS is a diagnosis of exclusion. More significant causes of a paraprotein need to be considered and excluded first.

12.2.1 Myeloma

- May present with bone pain, lytic bone lesions, renal impairment, hypercalcaemia, anaemia, recurrent infections, and/or hyperviscosity.
- Arrange urgent admission if there is spinal cord compression, significant hypercalcaemia, or acute renal failure.

12.2.2 Lymphoma / CLL

- May present with lymphadenopathy, hepatosplenomegaly, B symptoms (weight loss, fevers, drenching sweats) and/or cytopenias.
- In addition to the above, CLL is associated with an elevated lymphocyte count (manage according to the lymphocytosis guideline).

12.2.3 AL Amyloidosis

- May present with: heart failure (typically a restrictive cardiomyopathy), proteinuria/nephrotic syndrome, unexplained gastrointestinal symptoms, peripheral neuropathy, carpal tunnel syndrome, and macroglossia.

12.3 INVESTIGATIONS

12.3.1 Bloods

FBC, U&E, creat, bone profile, immunoglobulins, protein electrophoresis, serum free light chains

12.3.2 Urine

Bence Jones Protein (BJP)*, Albumin (or Protein) Creatinine ratio.

* NB. If a serum free light chain profile has been sent then urine for BJP is no longer necessary except if investigating for AL amyloidosis.

12.3.3 Tips for interpretation of immunoglobulins/paraproteins

- The paraprotein level refers to the size of the paraprotein (i.e. the protein electrophoresis result) not the total IgG/IgM/IgA level.
- **IgM paraproteins are usually associated with lymphoma whereas IgG/IgA paraproteins are usually associated with myeloma, but there is cross over. IgM myeloma is extremely rare.**
- A polyclonal hypergammaglobulinemia (i.e. global increase in IgG/IgM/IgA) with no paraprotein on protein electrophoresis is **not** a sign of myeloma. It is a non-specific finding in infective/inflammatory/reactive conditions and **does not need** haematology referral.

12.3.2 Tips for interpretation of serum free light chains:

SFLC (serum free light chains) are only significant if there is a monoclonal increase in **either** kappa or lambda resulting in an abnormal ratio. A normal ratio is 0.26-1.65 if eGFR >60.

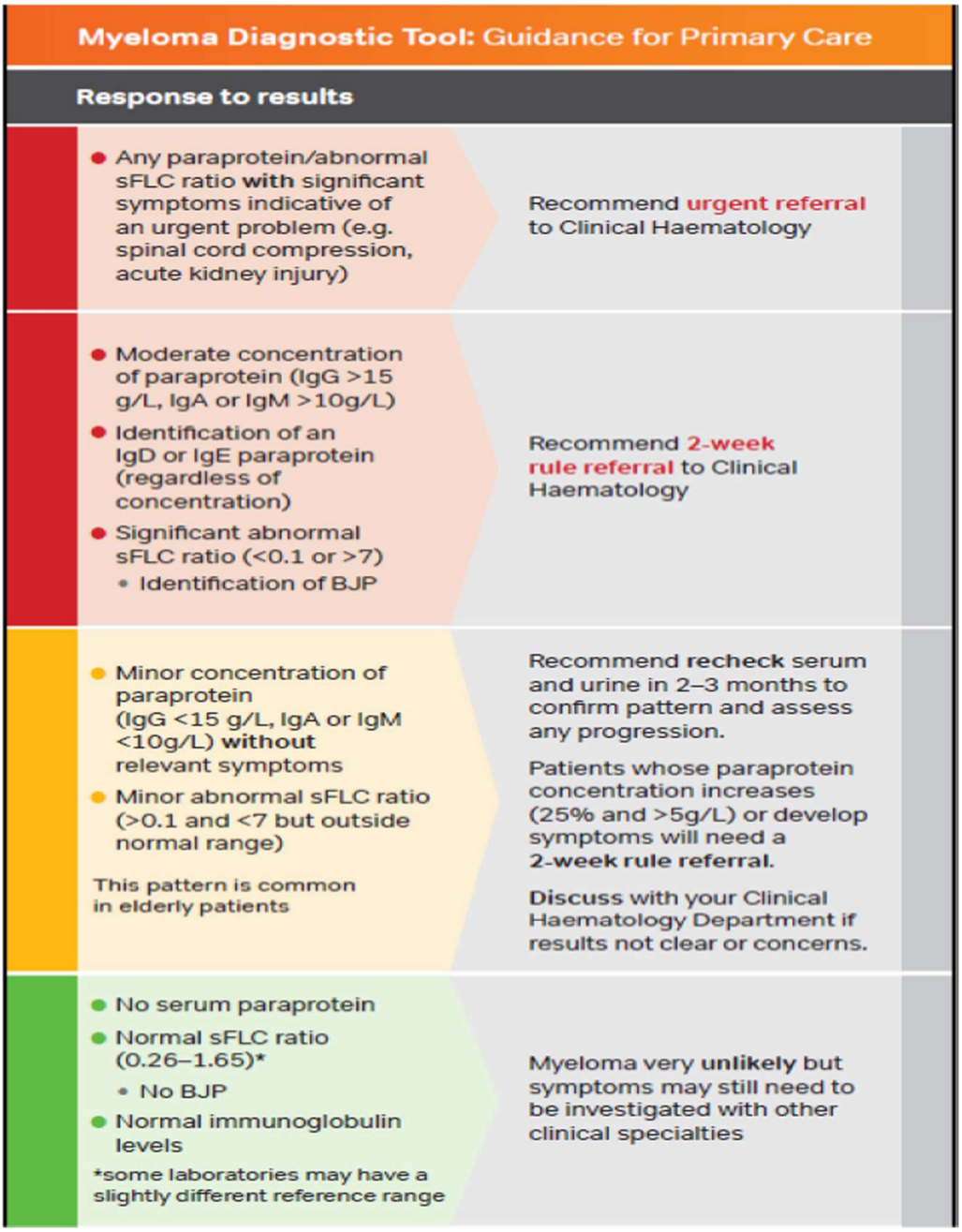
- An increase in both kappa and lambda with a normal ratio carries similar significance to a polyclonal hypergammaglobulinaemia and **does not need** haematology referral
- A ratio of 1.65-3.10 when eGFR <60 could be normal for renal dysfunction. Repeat in 3 months. Consider a haematology advice & guidance request if upward trend.
- If ratio is moderately abnormal:
    - 0.1-0.26
    - 1.65-7.0 with no background CKD
    - 3.1-7.0 with background CKD
- Consider a haematology advice and guidance request for oversight of onward management.
- Consider 2 week wait referral if clinical symptoms or other results strongly suggest myeloma.
- If ratio is <0.1 or >7.0 in an asymptomatic patient with otherwise normal/stable blood results, send a haematology advice & guidance request for oversight of onward management.
- If ratio is <0.1 or >7.0 in a patient with symptoms or abnormal blood results suggestive of myeloma, send a haematology 2 week wait referral.

12.4 REFERRAL CRITERIA

See table below for guidance

NB. A paraprotein >15 and/or light chain ratio <0.1 or >7.0 is not diagnostic of myeloma. If this is the only blood abnormality in an otherwise asymptomatic patient then please seek advice and guidance from haematology in preference to a 2 week wait referral.

Investigation and management of monoclonal gammopathy of undetermined significance. A British Society for Haematology Good Practice Paper – Stern et al Br J Haematol. wileyonlinelibrary.com/journal/bjh 2023; 202:734-744



12.5 MANAGEMENT OF MGUS

All patients with MGUS can be risk-stratified according to 3 risk factors:

- Paraprotein level >15g/l
- Abnormal serum free light chain ratio (<0.26 or >1.65)
- Non-IgG paraprotein

Number of risk factors present	Risk category	Risk of progression at 20 years
0	Low	5%
1	Low-Intermediate	21%
2	High-Intermediate	37%
3	High	58%

All patients should be given information and educated in what symptoms to report e.g.

https://www.myeloma.org.uk/wp-content/uploads/2023/04/Myeloma-UK-MGUS-Infosheet.pdf

12.5.1 Low / Low-Intermediate risk MGUS

Newly diagnosed patient with low or low-intermediate risk MGUS do not require secondary care referral unless they meet the criteria above. They do not require bone marrow biopsy or imaging.

Monitoring will be dependent on your local Trust policy, with some hospitals offering haematology-led remote tracker clinics whilst others rely on primary care monitoring.

12.5.2 Suggested monitoring for low / low-intermediate risk MGUS

Newly diagnosed MGUS patients should have FBC, creatinine, calcium, paraprotein and serum free light chain levels performed 6 months after diagnosis with annual follow-up thereafter, although the interval can be longer for low-risk MGUS and further investigations reduced if life expectancy is short.

Consider discussion with haematology if:

Paraprotein (not the total immunoglobulin subtype value) increases by 25% between monitoring bloods

An increase in paraprotein of 5g/l or involved light chain by 100mg/l between monitoring bloods

Development of symptoms of myeloma/lymphoma/amyloid, or development of otherwise unexplained hypercalcaemia, renal impairment or anaemia

Results meet any of the original 2 week wait referral criteria above

12.5.3 High-intermediate / High risk MGUS

The current recommendations are that high-intermediate and high risk MGUS should undergo secondary care investigations and work-up with high risk MGUS having ongoing secondary care monitoring. However this should be clearly individualised. It is therefore suggested that all high-intermediate / high risk MGUS not meeting the above referral criteria are, in the first instance, referred for haematology advice and guidance.

If referred back to primary care for ongoing monitoring then suggested monitoring frequency is