A002 - ADVICE ABOUT PATIENTS WITH PARAPROTEINAEMIA

What is a paraprotein?

A paraprotein is an abnormal protein secreted by a clone of plasma cells or lymphocytes. It is usually an intact, complete IgG, IgM or IgA immunoglobulin. IgD and IgE paraproteins are rare. Sometimes only light chains are secreted (20% of cases). Although it can be associated with myeloma or lymphoma, a paraprotein is more commonly a manifestation of a condition called Monoclonal Gammopathy of Undetermined Significance (MGUS).

How common is it?

Paraproteinaemia without any evidence of a local or systemic disorder occurs in:

- 0.3% of the normal population <50 years
- 1% of the normal population >50 years
- 3% of the normal population >70 years
- 10% of the normal population >80 years

Rarely, paraproteins are transient and associated with infections. Small paraproteins may be associated with connective tissue disorders, Hepatitis C and skin diseases. The prevalence of MGUS is increased in people of Afro-Caribbean ethnicity, those with occupational exposures to pesticides and immunocompromised patients (HIV infection, transplant recipients).

What happens with time?

Approximately 65% of patients presenting with paraproteinaemia do not have a demonstrable cancer and are described as having MGUS

- Approximately 1% per year will develop a myeloma or low grade lymphoma
- IgG, IgA and light chain MGUS can progress to myeloma or primary amyloidosis (rare)
- IgD and IgE paraproteins are rare and may progress to myeloma
- IgM paraproteins can progress to low grade lymphoproliferative disorders - lymphoma, CLL. IgM myeloma is exceedingly rare

What initial clinical assessment is required in patients found to have a paraprotein?

This should focus on the possibility the patient has myeloma, lymphoma or rarely primary amyloidosis.

- if hypercalcaemia, renal failure, symptoms of anaemia or bone pain ('CRAB') consider myeloma
- if lymphadenopathy, hepatosplenomegaly, weight loss, drenching sweats or fevers, consider lymphoma
- if large tongue (macroglossia), unexplained heart failure, peripheral neuropathy, carpal tunnel syndrome or nephrotic syndrome, consider primary amyloidosis

What further initial investigations are required in patients where a paraprotein is identified?

- FBC – checking for anaemia (and for a lymphocytosis in patients with an IgM paraprotein)
- calcium and bone biochemistry
- renal function
- serum free light chains (except in patients with an IgM paraprotein)
- test urine for protein (to exclude nephrotic syndrome)
- imaging of areas of bony pain e.g. MRI

When is a paraprotein "benign" or of "undetermined clinical significance" (MGUS)?

A paraprotein can be regarded as "benign" in asymptomatic patients if FBC*, calcium and renal function are normal and there are no lytic lesions on any imaging performed. The rest of the immunoglobulins are often normal (no immune paresis). This is especially true of small paraprotein bands (<10g/L) found by chance. At this stage patients do not require bone marrow examination or imaging of the whole skeleton.

*If lymphocytes raised with IgM see lymphocytosis advice sheet.

Serum Free Light Chain (SFLC) assay and urine testing for Bence Jones protein (BJP)

- The serum free light chain (SFLC) assay, which measures BJP in serum has replaced urine BJP.
- The individual levels of kappa or lambda light chains are of less importance than the kappa/lambda ratio. A ratio greater than 8.0 or less than 0.125 should lead to consideration of increased risk of Myeloma and referral to Haematology.
- SFLC can be used to diagnose light chain only myeloma (i.e. patients with myeloma who do not have a paraprotein). Light chain myeloma accounts for ~ 15% of myeloma cases.
- SFLC ratio is useful to identify MGUS patients at first presentation who have a low risk of progression to myeloma and can be monitored less frequently. It may also identify high risk cases which should be referred.
- The laboratory will routinely perform SFLC on all newly diagnosed paraproteins of non-IgM subtype.
- SFLC assay is not required as part of ongoing routine MGUS monitoring blood tests.

How should MGUS patients be monitored in primary care?

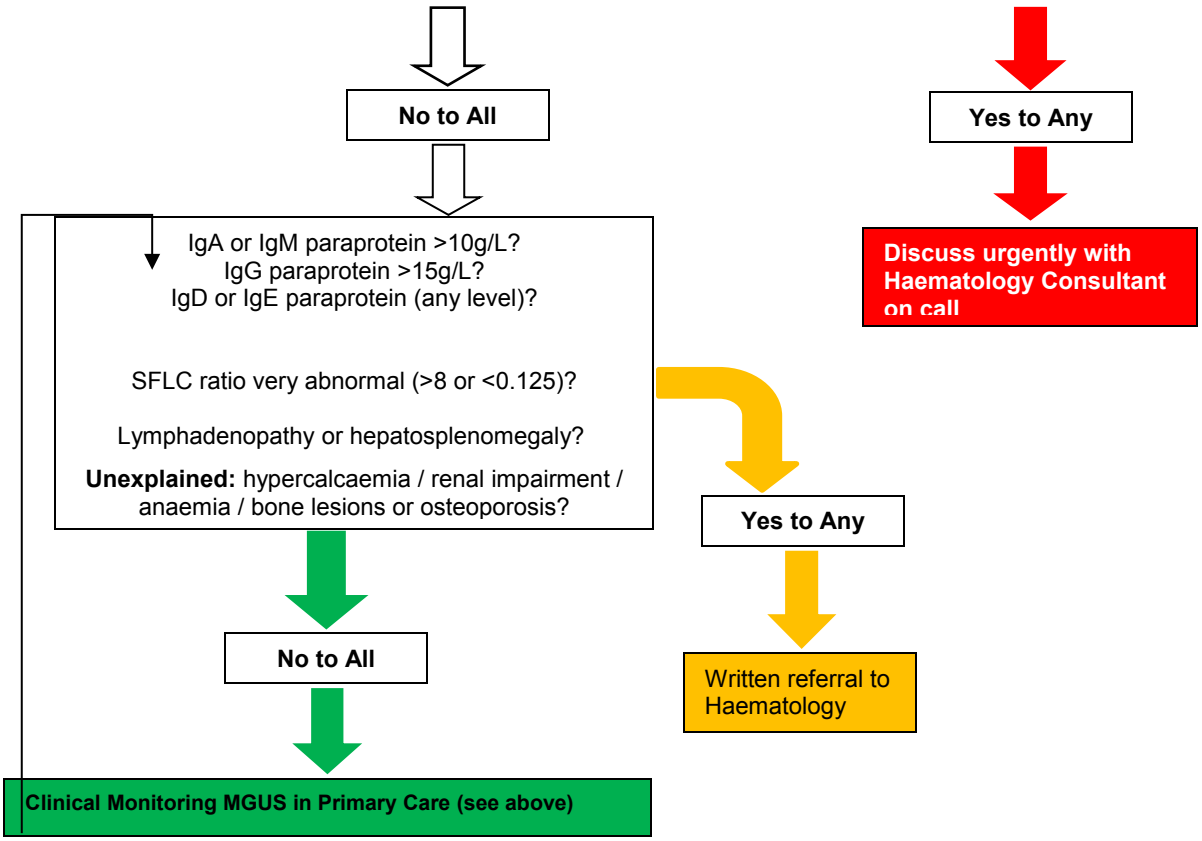
- Patients should only be diagnosed with MGUS after review of the clinical presentation and other laboratory results. New bone symptoms, lymphadenopathy, hepatosplenomegaly or unexplained anaemia, hypercalcaemia or renal failure may need referral to exclude myeloma or lymphoma
- There is limited evidence that monitoring MGUS for the early detection of haematological malignancy improves outcomes, however it is widely recommended.
- Guidelines recommend taking into account life expectancy. Patients with life expectancy < 5 years are unlikely to benefit from laboratory monitoring.
- For MGUS patients with long life expectancy (e.g. age < 50 years) consider referral for advice.

See table below for European Myeloma Forum 2014 guidance:

Paraprotein level* /SFLC	Monitoring advice
IgG paraprotein* < 15g/L and normal SFLC ratio *(5% absolute risk of progression at 20 years)*	**Either:** No further monitoring unless clinical concerns **Or:** Repeat paraprotein (not SFLC) FBC, UE, calcium in 6 months and then every 1-2 years (choice dependent on clinician/patient preference)
IgG paraprotein* < 15g/L and SFLC ratio < normal but > 0.125 or > normal but < 8)	Repeat paraprotein (not SFLC) FBC, UE, calcium in 6 months and then annually. Refer if paraprotein > 15g/L or if new clinical or laboratory concerns for haematological malignancy
IgA paraprotein* < 10g/L, SFLC ratio 0.125 – 8	Repeat paraprotein (not SFLC), FBC, UE, calcium in 6 months and then annually. Refer if paraprotein > 10g/L or if new clinical or laboratory concerns for haematological malignancy
No paraprotein and abnormal SFLC ratio but SFLC ratio <8 and >0.125 (i.e. light chain MGUS)	Repeat SFLC, FBC, UE, calcium in 6 months then annually.
IgM paraprotein* < 10g/L	Repeat paraprotein and FBC annually. Refer if > 10gL or if clinical concerns of lymphoma

*NB It is the total paraprotein result which guides action limits, not the specific immunuoglobulin level

Who should be referred?



If there are any queries please contact the duty haematologist for local hospital

What written information can I give a patient with MGUS?

The MGUS information sheet from Myeloma UK https://www.myeloma.org.uk/documents/monoclonal-gammopathy-of-undetermined-significance-mgus-infosheet

References

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