Guidance for users: Investigation of newly detected M-proteins and management of monoclonal gammopathy of undetermined significance (MGUS)

In 2009, the UK myeloma forum (UKMF) and the Nordic Myeloma Study Group (NMSG) produced guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). M-proteins are frequently detected in patients who are under the care of a general practitioner or a non-haematologist. The objective was to provide guidance to healthcare professionals who are often uncertain how to appropriately manage these patients in primary care.

The guidelines summarised below refer only to those patients defined as monoclonal gammopathy of undetermined significance (MGUS) with a newly detected M-protein.

Laboratory procedure at St Helier Hospital for the investigation of suspected M-proteins

An M-protein (otherwise known as a paraprotein) is a monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells. An M-protein can be whole immunoglobulin or fragments of immunoglobulin e.g. free light chain.

At St Helier Hospital screening for suspected M-proteins is carried out by the Immunology Laboratory. As part of the screening procedure for serum M-proteins immunoglobulin levels are measured and protein electrophoresis is performed. Upon detection of an abnormal finding the laboratory will perform immunofixation to confirm the presence of a serum M-protein and to determine the immunoglobulin class and light chain type. At this point the laboratory will quantify the M-protein concentration. If a urine sample has been provided electrophoresis will be performed as a screen for free light chains in the urine (Bence-Jones protein-BJP). Identification of the BJP will be determined by immunofixation. It is recommended that the requesting clinician provides the laboratory with both a serum and urine sample.

If no M-protein is identified as part of the initial screen and there is high clinical suspicion of non-secretory, light chain (AL) amyloidosis or light chain (LC) myeloma the laboratory will measure serum free light chains (SFLC).

Laboratory procedure at St Helier Hospital following identification of a new M-protein

Immunology will inform the Haematologists of any patients who meet the following criteria:

- serum M-protein ≥10g/L
- identification of an IgD or IgE M-protein (regardless of concentration)
- abnormal SFLC ratio
- identification of BJP
- serum M-protein <10g/L where clinical details indicate signs or symptoms suggestive of myeloma related organ or tissue impairment (ROTI)

If patients meet the above criteria the Haematologists will advise the requesting clinician on the initial management of the patient. The advice can vary from suggesting monitoring in primary care to referring the patient to the Haematology clinic.

Monoclonal gammopathy of undetermined significance (MGUS)

MGUS is defined as a serum M-protein <30g/L, <10% clonal plasma cells in the bone marrow and the absence of end organ damage that can be attributed to the plasma cell disorder. End-organ damage is characterised by hypercalcaemia, renal insufficiency, anaemia and bone lesions caused by the plasma cell disorder. MGUS is a diagnosis of exclusion. Patients will be classified as MGUS following the exclusion of myeloma, AL amyloidosis, Waldenström's macroglobulinaemia and other conditions associated with monoclonal immunoglobulins. MGUS is uncommon below the age of 50 years but the prevalence increases with age: 1-2% of individuals in their sixth decade have MGUS rising to 4-5% in their eighth decade. Additionally the prevalence is higher in African/Caribbean populations compared to Caucasians.

Consequently, the finding of a low level M-protein is common in the elderly population and the majority will be associated with MGUS. Swedish studies have shown that approximately 70% of MGUS patients have an M-protein <10g/L. However, it is important to note that a proportion of myeloma patients will present at diagnosis with an M-protein <10g/L. In Swedish and UK cohorts this has been estimated at 7% and 5% respectively. Furthermore, other clinically important diseases such as AL amyloidosis, LC myeloma and solitary plasmacytoma can present with a low level M-protein. In fact both myeloma and amyloid are commonly missed diagnoses. Consequently upon detection of an M-protein, it is important for the requesting clinician to look for signs and symptoms associated with these monoclonal gammopathies regardless of the M-protein concentration identified.

Recommendations for the investigation of patients following the detection of an M-protein

What further tests will the Immunology laboratory conduct?

The SFLC ratio at diagnosis can act as an independent prognostic marker for patients with MGUS. At St Helier Hospital SFLC are automatically measured in all patients with a newly detected M-protein.

What additional investigations should be performed?

Listed below are a number of additional routine blood and urine tests that the requesting clinician should ensure are performed on all patients with a newly identified M-protein:

- spot urine for urinary protein excretion and urinary protein electrophoresis (if not already done)
- full blood count
- serum creatinine
- urea and electrolytes
- corrected serum calcium

Importance of clinical history and examination

Upon detection of an M-protein a detailed history and examination should be performed to determine the likelihood of a plasma cell disorder or a lymphoproliferative disease. These should focus on symptoms, signs and test results that are commonly associated with myeloma, lymphoma or AL amyloidosis. As discussed previously a low level M-protein is more likely to be associated with MGUS; however AL amyloidosis is often associated with a low level M-protein and a low level M-protein does not exclude myeloma. If the patient has any signs or symptoms suggestive of underlying myeloma, other lymphoproliferative diseases or AL amyloidosis they should be

referred to a Haematologist for further investigation. This is also the case in patients without symptoms but with unexplained abnormal investigations results e.g. anaemia, renal impairment, hypercalcaemia, lytic lesions or osteoporosis on X-ray.

Prognosis and risk of malignant progression

Individuals diagnosed with MGUS have an increased risk of progression to malignant disorders including multiple myeloma, Waldenström's macroglobulinaemia, AL amyloidosis and lymphoproliferative disorders. The overall risk of malignant transformation is approximately 1% per year.

In order to predict those patients at greater risk of malignant progression several factors have been identified that are associated with a poorer prognosis:

Level of M-protein

The higher the M-protein concentration at diagnosis the greater the risk of malignant progression. It has been estimated that the risk of progression 10 years after MGUS diagnosis is approximately equivalent to the initial M-protein level. For example a patient with an initial M-protein level of 20g/L has a 20% chance of progression to multiple myeloma 10 years after diagnosis.

Type of M-protein

Both IgA and IgM M-proteins are associated with an increased risk of progression compared to IgG M-proteins.

SFLC ratio

An abnormal SFLC ratio at diagnosis has been shown to be associated with an increased risk of progression that is independent of the concentration and type of M-protein. Research has found that the risk of progression at 20 years was 35% with an abnormal SFLC ratio compared to 13% with a normal SFLC ratio.

A risk stratification model has been proposed based on the concentration of the M- protein, type of M-protein and SFLC ratio:

Risk Group		Risk of progression at 20 years (%)
Low	Serum M protein < 15g/L, IgG subtype, normal SFLC ratio	5
Low-intermediate	Any 1 factor abnormal	21
High-intermediate	Any 2 factors abnormal	37
High	All 3 factors abnormal	58

Table 1: Proposed risk stratification model to predict progression of MGUS (modified from Rajkumar et al. Blood, 2005)

This model may enable the identification of those patients who require more vigilant monitoring. Currently the UKMF and NMSG guidelines state that these findings need to be confirmed by additional studies before this risk stratification model can be applied to all newly diagnosed MGUS patients. However, individually these risk factors (type of M-protein, level of M protein and SFLC ratio) act as important prognostic markers in MGUS and it is recommended that all 3 factors are measured at diagnosis.

Monitoring MGUS patients in primary care

Patients diagnosed with MGUS will require continuous monitoring as the risk of malignant progression will remain throughout their lifetime. Given that the disease is frequently diagnosed in the elderly it is likely that these patients will die from co-morbidities rather than malignant transformation. The aim of monitoring is to identify those patients progressing to a malignant disorder prior to development of irreversible lytic bone disease, renal failure and other debilitating symptoms that would negatively impact on the effectiveness of treatment. As the pattern of disease progression is variable it is important to monitor both clinical symptoms and laboratory markers.

How frequently should MGUS patients be followed up?

No evidence has been published on which to base frequency of follow-up. However it can be argued that younger patients with longer life expectancies and a higher M-protein level should be monitored more frequently than those with a lower M-protein level and shorter life expectancy.

Following identification of a newly detected M-protein it is recommended that MGUS patients should be monitored every 3-4 months for the first year followed by 6-12 monthly as long as there are no symptoms suggestive of malignant progression. Both the clinician and the patient should be aware of relevant clinical symptoms; furthermore the patient should be educated and prompted to report these outside appointment visits if necessary.

At each monitoring appointment the patient must be clinically assessed and the following blood tests carried out:

- quantification of the M-protein and serum immunoglobulins
- full blood count
- serum creatinine
- urea and electrolytes
- corrected serum calcium

Further Investigations/Referral to Haematology

The UKMF and NMSG guidelines recommended that MGUS patients should be referred for specialist advice if any of the criteria below are met:

- concentration of the M-protein increases by more than 25% (a minimum absolute increase of 5g/L)
- development of symptoms compatible with a diagnosis of myeloma or lymphoma
- development of unexplained anaemia, other cytopenias, abnormal renal function or hypercalcaemia

Please refer to our flow chart for a summary of the recommended algorithm used by St Helier Hospital.

References

- Bird J, Behrens J, Westin J, Turesson I, Drayson M, Beetham R, et al. UK Myeloma (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). British Journal of Haematology. 2009; 147: 22-42.
- Rajkumar VS, Kyle RA, Therneau TM, Melton JL, Bradwell AR, Clark RJ. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005; 106: 812-817.
- Kyle RA, Durie BGM, Rajkumar SV, Landgren O, Blade J, Merlini G et al. Monoclonal gammopathy of undetermined significance (MGUS) and smouldering (asymptomatic) multiple myeloma: IMWG concensus

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