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Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smouldering Myeloma (SMM): A Practical Guide to Management

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Abstract

Monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM) are precursor conditions of symptomatic multiple myeloma (MM). Diagnostic principles are aimed at excluding MM requiring therapy, other conditions associated with paraproteins that may require different management, and risk stratifying patients for the purposes of tailored follow up and investigation. The IMWG have recently published a revised definition of MM, that singles out a small group of patients with SMM who are at very high risk of progression and organ damage; such patients are now included under the definition of MM, and recommended to start anti-myeloma treatment. Furthermore, the recently published NICE guideline recommends cross sectional imaging techniques in place of skeletal survey. These recent recommendations are discussed, and practical guidance for investigation and management presented.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) describes the presence of a serum monoclonal protein (paraprotein) without other evidence of multiple myeloma (MM), Waldentrom's macroglobulinaemia (WM), amyloidosis or other lymphoproliferative disorder[1]. MGUS is thought to consistently precede the development of MM[2], but not all patients with MGUS have the same risk of progression to MM. Many paraproteins are picked up incidentally and the challenge is how best to manage these patients whilst avoiding over investigation and/or incurring undue anxiety[3]. Risk models for progression can be incorporated into management algorithms for these patients.

Smouldering myeloma (SMM) is an intermediate stage between MGUS and symptomatic MM[4]. Patients with SMM have a higher initial risk of progression compared to MGUS patients but risk reverts to MGUS levels after 10 years. Median time to progression is around 4.8 years[5]. SMM patients lack evidence of end organ damage, but a small proportion may warrant treatment on the basis of high risk biomarkers[6].

Epidemiology and pathophysiology

The overall risk of progression of MGUS is approximately 1% per year[7], and remains unchanged over many years although many are elderly and will die from unrelated conditions[8]. Prevalence increases with age (3.2% over 50years), is higher in males and in Africans[9][10]. IgG is the commonest subtype (68.9%)[11]. MGUS is associated with diverse conditions including autoimmune and inflammatory conditions, liver disease, bone

marrow and organ transplantation[12][13]. The aetiology is unclear, suggested predisposing factors include family history of haematological malignancy, immunosuppression, radiation exposure and pesticides[14, 15]. SMM has a similar age of presentation as MGUS and symptomatic MM (60-70years), and is most commonly IgG (74%) or IgA (22.5%) [5][16].

Founder genetic events in MM such as chromosomal translocation into the IgH gene loci and hyperdiploidy are present in MGUS. Secondary genetic lesions occurring in sub-clones that compete for dominance may lead ultimately to clonal progression and expansion of certain "fitter" sub clones. Common secondary events that are associated with the progression to symptomatic MM include point mutations in oncogenes (eg. N-RAS, K-RAS, TRAF3, p53), MYC up regulation by a variety of mechanisms, and chromosome 1 imbalance (1q gain or 1p loss). A progressive increase in the incidence of copy number abnormalities and epigenetic modifications may occur [17] [18].

Definition of MGUS

All criteria must be met:

1. Serum monoclonal protein <30 g/L
2. Clonal bone marrow (BM) plasma cells (PC) <10%,
3. Absence of end-organ damage (hypercalcemia, renal insufficiency, anaemia, and bone lesions) [19].

MGUS Related Disorders and associated risks

MGUS can be associated with other clinically significant conditions, listed in Table 1 [20], including AL amyloidosis, MGUS of renal significance (MGRS), type I and II cryoglobulinaemia, cold agglutinin disease and autoimmune neuropathies, the latter usually caused by autoantibody activity of an IgM paraprotein. Other rare diseases associated with monoclonal gammopathy include POEMS syndrome, scleromyxoedema, acquired Fanconi syndrome and Schnitzler syndrome [21, 22]. Individuals with MGUS have an increased risk of osteoporosis, venous/arterial thrombosis, infections, as well as an increased risk of developing myeloid and non-haematological malignancies [23] [24] [25].

Definition of Smouldering MM including recent revisions

In 2003 IMWG developed the first international consensus guidelines that classified SMM as BMPCs ≥10% and/or paraprotein (PP) ≥30 g/L) and critically the absence of CRAB

features (high calcium, haemoglobin 2g/dL below normal or <10 g/dL, lytic bone lesions or osteoporosis with compression fractures, symptomatic hyperviscosity, amyloidosis, or >2 bacterial infections/12 months) [16]. As there was no evidence that treatment of asymptomatic SMM patients altered the natural disease history or improved long term outcomes, treatment was withheld unless progression occurred as defined by end organ damage.

Revised criteria

It became clear that some SMM patients are at very high risk of progression to symptomatic MM[18], moreover, progression was associated with marked morbidity. Hence, work was done to identify patients at ultra high risk (approximately 80%) of progression within 2 years. Three markers identify patients at ultra high risk of progression (80% over 2 years) [6]:

Additional new criteria for diagnosis of myeloma (Table 2)

- *Bone marrow plasmacytosis*

BMPCs of ≥60% (present in <5% of patients) carries a very high risk of progression to MM (>80% within 2 years)[26, 27], and is thus now considered a MM defining criterion.

- *Serum Free Light Chains*

High serum free light chains are a risk factor for progression in SMM [28], and SFLC ratio of >100 carries a 2-year progression risk of 72%[29], and is now a MM defining criterion.

- *Focal lesion/s on MRI*

MRI is now recommended for screening in SMM (see below). Patients with >1 focal lesion on MRI had a 70% risk of progression at 2 years)[30], findings subsequently confirmed [31, 32]. Thus >1 focal lesion on MRI is now a MM defining criterion. For patients with solitary bone lesions, data are less clear and regular (3-6 monthly) follow up by MRI is recommended.

Table 2 summarises these new MM defining features, for which anti-MM treatment is recommended. Alongside these recommendations, revised definitions of organ damage have also been produced (Table 3). The term symptomatic MM should now be dropped, in favour of MM, to include asymptomatic patients who require treatment on the basis of one

or more MM defining criteria. Hence SMM, previously used to refer to "symptomatic MM" should now be used exclusively to refer to smouldering MM, or asymptomatic MM.

Risk factors for Progression in MGUS

Presenting features and dynamics of the clone during follow up are helpful predictors of progression. Recognised risk factors include:

a. Level of the monoclonal protein [33].
b. Level of BMPCs (>5%)[34].
c. Rise in paraprotein over time [35].
d. Abnormal SFLC ratio [36].
e. Biological characteristic of the MGUS clone, higher for IgA/IgM than for IgG. [11, 33].

Fluorescent-in-situ-hybridisation (FISH) defined abnormalities including recurrent primary IgH translocations and hyperdploidy are found in MGUS [37], but it is unclear if specific abnormalities eg. del(17p) are predictive of progression to MM.

Risk models in MGUS

Patients are risk stratified using clinical variables identified in epidemiological studies, and two main prognostic models are the Mayo clinic model, and the PETHEMA group or Spanish model (Table 4). [36] [38].

Risk Stratification Models in SMM

The main risk models for SMM reflect those in MGUS (Table 4). The Mayo clinic model included abnormal SFLC ratio, paraprotein level and BM plasmacytosis, while the Spanish group used a flow cytometry based model with two independent variables [39].

Need for new risk models in SMM

Revision of diagnostic criteria for MM that remove the ultra high risk SMM patients requires a re-evaluation of our risk models for SMM. Genetic abnormalities [deletion 17p, t(4;14)] or gene expression signature may be important [31, 40, 41], as may PET-CT findings [42]. The presence of Bence Jones proteinuria (especially >500mg/24 hours) or rising paraprotein (evolving SMM) may also impart greater risk of progression [43]. Immunophenotype, circulating plasma cells, a high PC proliferative rate have also been implicated [31]. All these need to be studied in larger patient cohorts to assess their wider applicability.

Diagnosis of MGUS

The major aim of investigating these patients is to distinguish between MGUS, SMM and MM requiring treatment. The commonest reason for assigning a diagnosis of SMM (rather than MGUS) is the presence of ≥10% plasma cells in the bone marrow. For IgM and light chain only conditions, the equivalent is called smouldering WM, and idiopathic Bence Jones proteinuria, respectively. It is also important to differentiate MGUS of truly no clinical significance from MGUS associated with amyloidosis, Waldenstrom's macroglobulinaemia (WM) and other lymphoid neoplasms. Symptoms should also be sought for the rarer disorders associated with a paraprotein e.g. POEMS syndrome. (Table 1)

All patients require history and examination, full blood count, renal function, total protein, serum calcium, serum and urine protein electrophoresis with immunofixation and serum free light chains. A bone marrow aspirate and trephine biopsy (BMAT) should be performed when serum PP ≥ 15g/L, if non IgG MGUS, abnormal SFLC ratio (> 10 or < 0.10), or if diagnosis of MGUS is in doubt. All patients with suspected myeloma (paraprotein > 30g/l or bone marrow plasma cells >10%) need cross-sectional imaging as per recent NICE guidelines: whole body MRI as first line or whole body low dose CT. [50]

For high risk MGUS patients (Mayo clinic model), a skeletal survey should be carried out (or a CT chest abdomen and pelvis in IgM MGUS). MRI or PET-CT imaging is not recommended outside the context of a clinical trial [44].

Management of MGUS

Clinical trial results show no benefit for early intervention, and the risk of progression to MM is low, thus current management is 'watch and wait' [45]. As risk of progression does not change over time lifelong follow up is recommended, with monitoring tailored to patient's risk of progression, co-morbidities and life expectancy.

Risk stratification of patients (Mayo clinic model) into low, intermediate and high risk MGUS aids counselling and follow up [46]. Current practice will vary from centre to centre. Based on currently available evidence and guidelines a reasonable approach is:

Low risk: SS and BM not required, monitor every 6 months for 2 years then 1-2yrly if stable. Monitoring can be done in primary care and should include patient review, blood count, renal function, calcium, and paraprotein level.

Intermediate or high risk: SS and BM are mandatory, review and monitor as above every 6 months for 2 years then annually for life. Follow up should include history and examination, full blood count, renal function, calcium and paraprotein. Monitoring should be initially in secondary care, but after 5 years, primary care monitoring is reasonable. Although the risk of progression in patients with light chain only MGUS is relatively low (0.3% per year), there is a considerable risk of developing renal disease, hence 6-monthly follow up is recommended [11]. Finally, MGUS patients with elevated SFLC should be monitored for development of amyloidosis or MGRS, hence measurement of NT-proBNP and urine albumin at follow up is recommended [19].

A BMAT +/- skeletal survey is always indicated if features suggestive of end organ damage develop or if >25% increase in PP levels occurs over a three month period (minimum 5g/L). Diagnostic work up and management plan should be altered according on age and co-morbidities (Figure 1). For example in a person of advanced age with limited life expectancy it may be reasonable to omit SS and BMAT from the work up or not to undertake regular monitoring of the paraprotein level. Whichever risk group a patient falls into, it is important to provide information and counselling as the diagnosis may lead to anxiety and fears for the future. MyelomaUK provide written information and telephone advice:
http://www.myeloma.org.uk/information/myeloma-uk-publications-list/other-related-conditions/mgus-infosheet/

Diagnostic Investigations for SMM

Investigations are aimed at differentiating SMM from symptomatic MM requiring treatment. All patients need baseline blood counts, renal function, serum calcium and total protein, serum and urine protein electrophoresis with immunofixation and serum free light chains. Risk stratification of SMM may be useful, eg. the Mayo clinic model. All patients with a paraprotein >30g/L and/or SFLC ratio >8 should be considered for further testing with BM and imaging. As per NICE guidance, skeletal survey is no longer sufficient and cross-sectional imaging is recommended, with the choice of MRI, low-dose whole-body CT or PET-CT being made according to local practice [47].

Treatment for SMM

Historical studies have shown no advantage to initiating treatment for patients with SMM, largely due to lack of efficacy and high toxicity of regimens used.[48] [49][50]. Recently, a

randomised trial has indicated, for the first time, that treatment in SMM can improve outcomes. This Phase III trial used flow cytometry to identify high risk patients and prospectively randomised them to receive treatment with lenalidomide and dexamethasone versus observation only. With median follow-up of 40 months, treated patients had significantly longer time to progression (median not reached vs. 21 months) and overall survival (3-year survival 94% vs. 80%) [51]. Drawbacks of the study are the criteria used to risk stratify, and the unexpectedly high rate of death in the control arm. Several trials are currently evaluating new drugs and strategies in high risk SMM, and such patients should be considered for entry into clinical trials otherwise observation still remains standard of care.

Monitoring patients with SMM

The risk of progression in SMM is highest in the first years after diagnosis, maximal in the first two years, and reducing over the next few years. Hence, the monitoring needs to be more frequent soon after diagnosis and can become less frequent 5 years after diagnosis. There are no formal prospective studies of monitoring in SMM. As per NICE guidelines, patients should be monitored every 3 months initially [47]. Pragmatically, a reduced frequency of monitoring may be adopted after 2 years, depending on risk (Figure 2). Monitoring should include assessment of CRAB symptoms, FBC, renal function, bone profile, immunoglobulins, serum protein electrophoresis and SFLC if appropriate [47]. High risk patients, those with a rising paraprotein or new symptoms and those with a single focal lesion on MRI may need repeat imaging or bone marrow examinations.

Conclusion and Future Directions

MGUS is associated with a risk of progression to MM and a variety of other clinically significant conditions. Diagnostic work up of suspected MGUS patients should seek evidence of these. Risk stratification models can help with estimating risk of progression and, together with patient-specific factors, planning follow-up.

SMM is an area where on-going research is re-defining risk boundaries with implications for monitoring and treatment. As new factors for progression are identified, some patients will now be reclassified as MM requiring treatment, and there is a suggestion that early treatment of high risk SMM may be of benefit. While MM remains incurable, here is insufficient evidence, however, to recommend routine treatment of these asymptomatic patients, or indeed to indicate which treatment is the best. Progression to MM may not the

only important end point for treatment of SMM patients as pre-emptive therapy may promote the earlier out-growth of resistant disease, making the treatment of truly symptomatic disease more difficult. Genetics clearly define outcomes in MM, and may also impact outcomes of therapy in SMM. All these remain important questions to be addressed in prospective trials to refine our approach to SMM and guide treatment, meanwhile current guidance is confined to monitoring [47].

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Tables

Table 1. M-protein related disorders (other than AL amyloidosis) adapted [21]

Disorder	Clinical features and diagnostic tests
Light chain deposition disease (LCDD)	Usually kappa light chain, presenting with albuminuria and nephrotic syndrome
POEMS syndrome	Majority IgG lambda Peripheral neuropathy Organomegaly (liver, spleen, lymphadenopathy) Skin changes (cherry angiomata, changes in texture and pigmentation, alterations in body hair) Endocrinopathy (pancreatic, adrenal, gonadal, paarhyroid, pituitary) Ascites, pleural effusions, peripheral oedema Pappiloedema Sclerotic bone lesions Thrombocytosis, polycythaemia, thrombotic diathesis Elevated circulating vascular endothlial growth factor
Acquired Fanconi syndrome	Tubular proteinuria, glycosuria, amino aciduria. acidosis, hypophosphatemia Renal failure, osteomalacia Almost all kappa light chain
Cryglobulinaemia	Vasculitis, peripheral neuropathy, fatigue, renal failure, purpuric rashes, Raynaud's phenomenon, leg ulcers, acrocyanosis
Scleromyxoedema	Diffuse skin thickening, obstructive lung disease, pulmonary hypertension Usually IgG lambda
Schnitzler Syndrome	Chronic neutrophilic urticarial dermatosis Arthralgia, bone pain, lymph nodes, liver, spleen enlarged Usually IgM kappa
Xanthomatosis	Cutaneous xanthoma lesions (yellow papules) Usually IgG
Cold agglutinin disease	Haemolysis, Raynaud's phenomenon, acrocyanosis

Table 2: Definition of multiple myeloma, incorporating recent revisions [6]

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

Myeloma defining events*:*

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder as follows:

- Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: **creatinine clearance <40 mL/min† or serum creatinine >177 µmol/L (>2 mg/dL)**
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, **CT, or PET-CT‡**

Biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage* ≥60%
- Involved:uninvolved serum free light chain ratio§ ≥100
- >1 focal lesions on MRI studies¶

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg/24h and/or **clonal bone marrow plasma cells 10–60%**
- Absence of myeloma defining events **including biomarkers of malignancy** or amyloidosis

‡PET-CT=^{18}F-fluorodeoxyglucose PET with CT.

*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

†Measured or estimated by validated equations.

‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.

¶ Each focal lesion must be 5mm or more in size

Table 3. New Definitions of organ damage[6]

Myeloma bone disease One of PET-CT, MRI or low-dose whole body CT (depending on local practice) to be used at diagnosis in suspected smouldering myeloma. The detection of one or more sites of osteolytic bone destruction (>5mm) on PET-CT or low-dose whole-body CT meets the criteria for multiple myeloma requiring treatment. Osteoporosis and vertebral compression fractures alone are no longer sufficient for a diagnosis of myeloma. This is to avoid over diagnosing many elderly people with MGUS and osteoporosis. **Definition of renal failure** The 2003 IMWG criteria used a fixed creatinine level (> 173umol/L) to define renal insufficiency. New recommendation is to use measured or estimated GFR of <40ml/min instead for CRAB criteria. Only renal failure caused by light chain cast nephropathy is regarded as a myeloma defining event. A renal biopsy may be needed to exclude other causes of renal failure. **Bone marrow plasmacytosis** Either clonal BMPC ≥10% or biopsy proven plasmacytoma required for the diagnosis of MM.

Table 4. Risk models for MGUS, and for SMM

Model and risk factors	Number of factors	Progression risk
MGUS		
Mayo Clinic Model [35]		At 20 years
- non-IgG isotype	0	5%
- M-protein ≥15g/L	1	21%
- abnormal SFLC ratio	2	37%
	3	58%
PETHEMA model based on flow cytometry of bone marrow [338]		At 5 years
- Abnormal phenotype (aberrant plasma cells)	0	2%
- DNA aneuploidy	1	10%
	2	46%
SMM		
Mayo Clinic Model [26]		At 5 years
- abnormal SFLC ratio (<0.125 or > 8)	1	25%
- BM PCs ≥10%	2	51%
- PP ≥30g/L	3	76%
PETHEMA model based on flow cytometry [40]		At 5 years
- ≥95% abnormal bone PC/total BMPC	0	4%
- Immuneparesis	1	46%
	2	72%

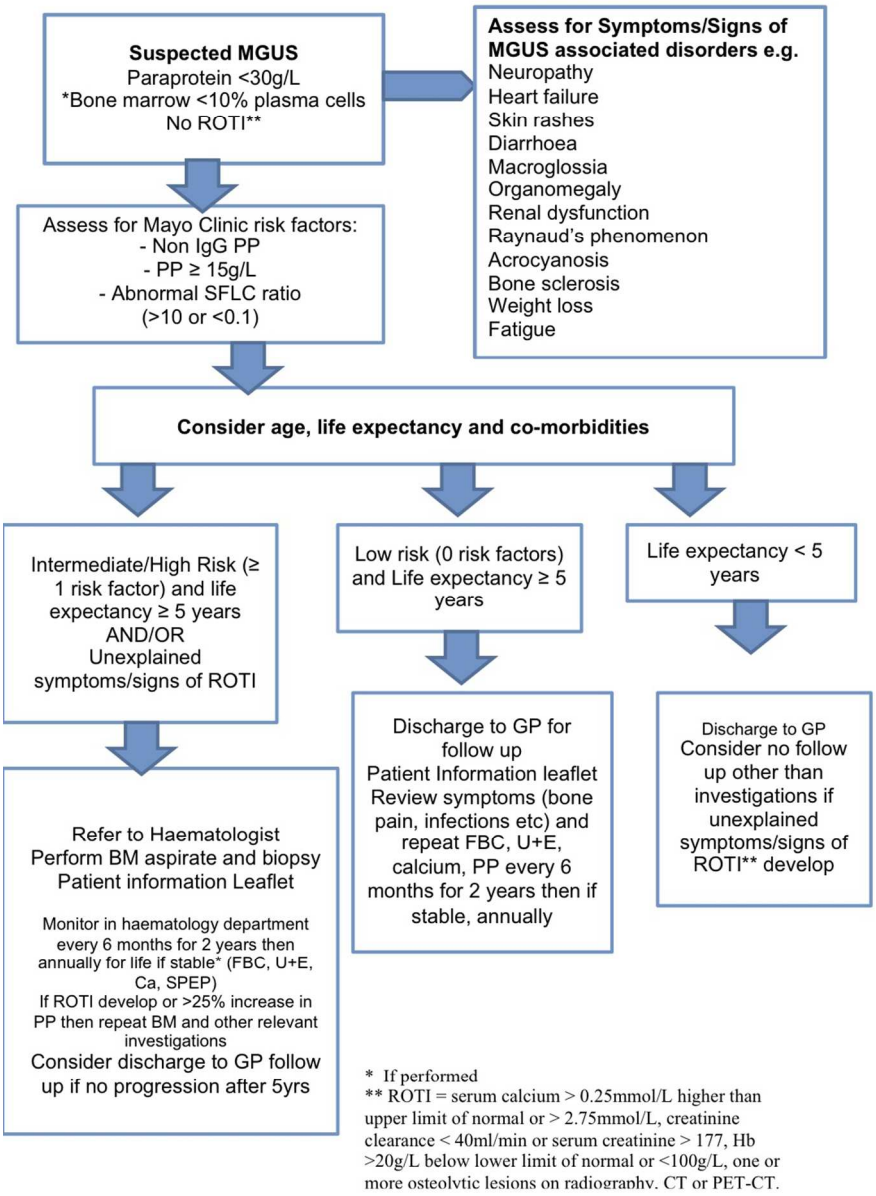
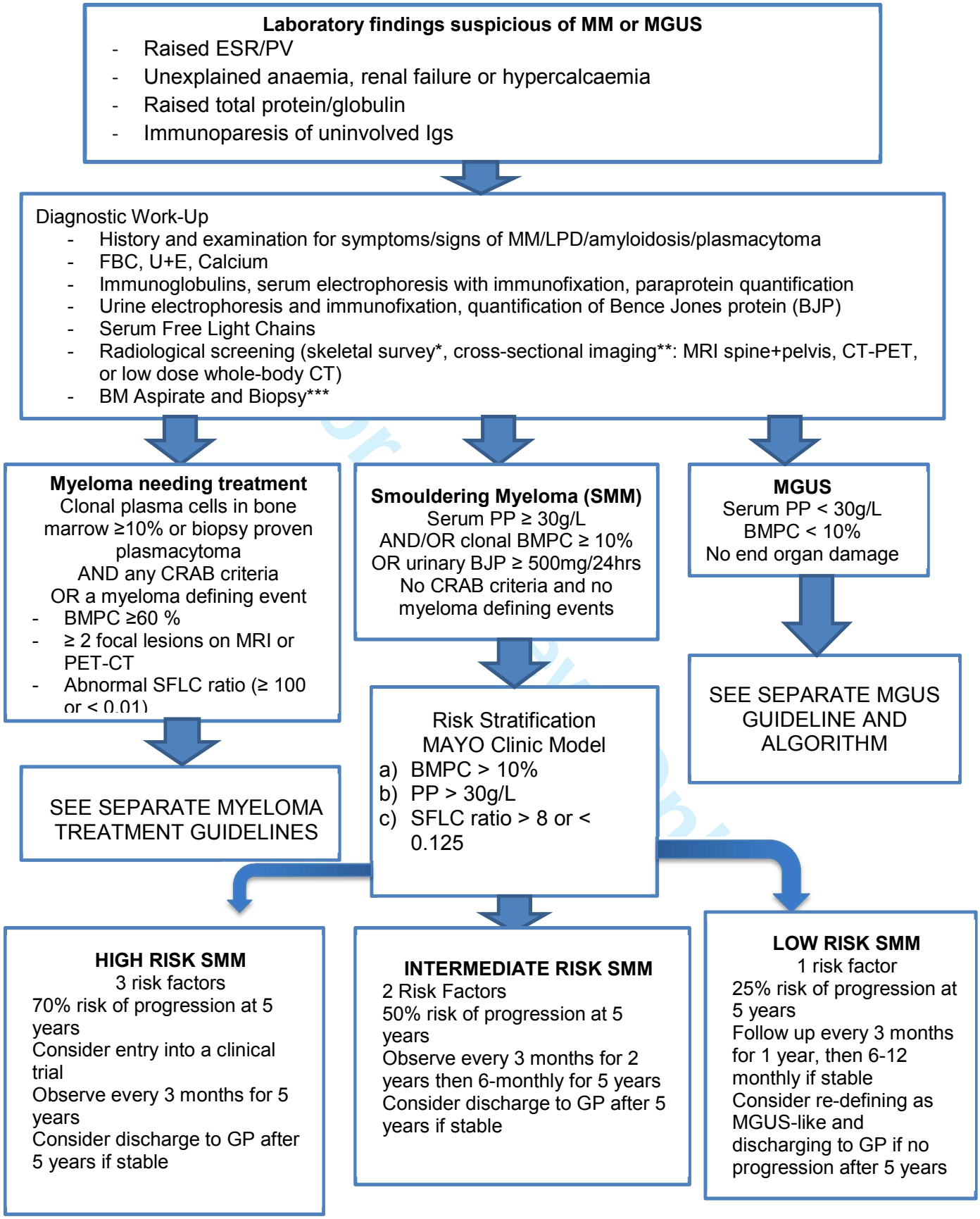


Figure 1. Algorithm for investigation and management of patients with suspected Monoclonal Gammopathy of Undetermined Significance (MGUS)

184x250mm (150 x 150 DPI)



* for high risk MGUS
** if pp>30 or LC ratio >8, choice of technique according to local practice
*** Required if non-IgG MGUS, pp ≥15g/L