

Review Article

Follow-up Care of Monoclonal Gammopathy of Undetermined Significance: A Guide for Primary Care Physicians

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Introduction

Monoclonal Gammopathy of Undetermined Significance (MGUS) is a condition in which M protein, an abnormal monoclonal immunoglobulin, is present in the blood at a nonmalignant level. Specifically, it is defined by: blood serum M protein concentration <3 g/dL (<30 g/L), $<10\%$ plasma cells in the bone marrow, and no evidence of end organ damage [1,2]. Evidence of end organ damage includes hypercalcemia, renal insufficiency, anemia, and bone lesions. These are indicative of MGUS progression and which can be attributed to the monoclonal plasma cell proliferative process [3]. MGUS occurs in 3% of the general population older than 50 years. Incidence increases with age and varies with sex with higher rates observed in males than females [1,4].

MGUS is the most common plasma cell disorder, with 60% of patients that present to the Mayo Clinic with a monoclonal gammopathy being diagnosed with MGUS [3]. While it is typically an asymptomatic condition, it is premalignant disorder to other monoclonal gammopathies. Multiple Myeloma (MM) is almost always preceded by MGUS and the majority of patients will have detectable levels of M protein for at least 5 years prior to MM diagnosis [5,6]. MGUS also precedes immunoglobulin light chain (AL) amyloidosis and Waldenstrom Macroglobulinemia (WM) and tends to progress to disorders at a fixed but unrelenting rate of 1% per year [4].

Discussion of M Protein

M protein is produced by proliferation of cells in the B-lymphocyte lineage [1]. It can exist as a complete immunoglobulin with 2 heavy chains and 2 light chains or as a free light chain. M protein can also be categorized as IgM or non-IgM as differing cellular origin will produce IgM, IgG, or IgA variants. IgM MGUS is more likely to progress to lymphoma or WM, while non-IgM MGUS is more likely to progress to MM or AL [7].

Typically, M protein is an incidental finding during work up for another complaint. Routine screening for an M protein in the absence of clinical suspicion is not recommended due to the low risk of

malignant progression. However, once it is found, a comprehensive history, Physical Examination (PE), and laboratory tests (serum protein electrophoresis, serum immunofixation, serum free light chains, CBC, and serum calcium and creatinine) should be performed [8]. Serum protein electrophoresis will quantify substantial M protein concentrations, while serum immunofixation and serum free light-chain assay will detect lower levels of M protein and light chain M protein respectively. All 3 tests used together will give you 98% sensitivity for detection of serum m-protein [9].

At diagnosis, the presence of MM, WM, AL amyloidosis, and other MGUS-related disorders have to be excluded. In cases of significant proteinuria or renal insufficiency, kidney biopsy may be indicated [10]. After MGUS is confirmed, the patient should be risk stratified to determine the need for bone marrow biopsy and to predict the risk of progression [8].

Initial Follow-up: Risk Stratification

Previous studies [11,12] (A, B) have recognized subsets of patients with MGUS have different risks of progression to myeloma and other related disorders. Risk factors predicting progression are:

- Presence of non-IgG type M protein
- M protein concentrations >1.5 g/dL
- An abnormal free light-chain ratio

Based on these, MGUS can be classified into 4 risk categories: low, low intermediate, high intermediate, and high.

- Low risk: All 3 risk factors are absent
- Low intermediate: 1 risk factor present
- High intermediate: 2 risk factors present
- High risk: All 3 risk factors present

A patient classified as high risk using these criteria will have a 10-fold increase in risk of developing MM compared to a low risk patient. Half of patients with MGUS fall into the low-risk category, defined by IgG-type serum M protein in a concentration <1.5 g/dL and a normal serum free light chain ratio (kappa-lambda 0.26-1.65) [8].

Long Term Follow-up

Most recommendations regarding follow-up are based on expert opinion due to the lack of randomized data. Most experts agree that all patients should be re-evaluated six months after the M protein is detected, along with the following tests: CBC, serum creatinine, serum calcium, serum protein electrophoresis, and serum free light

chains [8].

Patients with low risk MGUS have a risk of progression of 5% in 20 years [13]. Low-risk patients with a stable M protein level who do not display clinical or laboratory evidence of myeloma or other disorders can be followed-up by Primary Care Providers (PCPs). After the six month reevaluation, they can be seen every two-three years [8]. These patients may be followed with history and PE, and repeating CBC, calcium, creatinine, and measurement of serum and urine M-protein [13]. All other patients (non-low risk and light-chain MGUS) should be followed at annual intervals with a history and PE, CBC, serum calcium and creatinine, and serum and urinary M-protein measurements [13].

Follow up visits should also include monitoring for myeloma-defining events. CRAB is helpful mnemonic for these events which include Calcium elevation (>1 mg/dL), Renal insufficiency (creatinine >2 mg/dL or creatinine clearance <40 mL/min), Anemia (hemoglobin <10 g/dL), and Bone lesions [14,15]. Elevation of serum M protein level above 3 g/dL and/or between 10% and 60% clonal plasma cells in the marrow with no end organ damage would indicate progression of MGUS to Smoldering Multiple Myeloma (SMM) [16]. SMM carries a significantly higher risk of progression to MM with 10% chance of malignancy annually for the first 5 years (51% rate of progression to MM or AL) [17]. Evidence of kidney dysfunction is concerning for progression Monoclonal Gammopathy of Renal Significance (MGRS). M protein can build up in the kidneys and eventually develop into deposits. Monoclonal protein deposits in the kidneys can be clinically indicated by increased protein or creatine levels and indicate progression to MGRS [8,18].

No follow-up may also be considered in elderly patients or patients with significant comorbidity with a short life expectancy (<5 years). These patients may only need laboratory investigations or bone marrow analysis only when symptoms suggestive of MM or related diseases develop [10].

A retrospective analysis of MGUS patients at Mayo Clinic (H) found that optimally followed (follow up visits at least every 24 +/- 12 months) of MGUS patients only led to diagnosis of MM before symptoms or significant complications in 16% of patients. However, an additional 25% of diagnoses before serious MM related complications came from workup of patient complaints. PCPs must constantly assess for and educate patients to report worrying symptoms (e.g. fatigue, neuropathy, weight loss, night sweats, and bone pain). This education is essential for early diagnosis of MGUS progression since these symptoms may present between follow-up visits [8,19]. Additionally, PCPs should be alert for signs and symptoms of AL amyloidosis such as restrictive cardiomyopathy, nephrotic range proteinuria, and hepatosplenomegaly [13].

Patients with MGUS have a decreased life expectancy and an increased risk of fractures, renal impairment (as seen in MGRS), cardiovascular disease, peripheral neuropathy, and recurrent infections [20,21]. Therefore, it may be appropriate to evaluate patients for excessive bone loss by using Dual-energy X-ray Absorptiometry (DXA), especially if other risk factors for osteoporosis are present. Patients with low bone mineral density or prevalent fractures can receive treatment with bisphosphonates, and also calcium and vitamin D supplementation if dietary intake is insufficient [10]. While

the link between MGUS and neuropathy is not entirely clear, IgM MGUS is most associated with demyelinating peripheral neuropathy and non-IgM MGUS is implicated in POEMS syndrome [22].

Referral to Specialists

Patients with intermediate and high-risk MGUS, abnormal serum free light-chain ratios, and those who show evidence of malignant progression should be referred to a hematologist. Patients with intermediate and high-risk MGUS could be referred for bone marrow biopsy before assessment by the hematologist. Additionally, if AL amyloidosis, WM or another M protein related disorder is suspected, referral to subspecialists is advised [8]. Any signs of renal insufficiency or proteinuria should prompt follow up with nephrologist for kidney biopsy to rule out MGRS [8,18]. MGUS patients with new cardiovascular or neurological complaints should also be referred to specialist for further evaluation and testing [21]. It is important to note that a recent study has found that levels of M proteins and the other markers may change over time, and thus it is important to reassess the patient's risk at each visit and refer accordingly [23].

Conclusion

MGUS is a premalignant condition with a steady rate of progression to multiple myeloma at a rate of 1% per year. Appropriate follow-up by PCPs can help mitigate superfluous healthcare spending while maintaining patient health and safety. All patients diagnosed with MGUS should be seen six months later. Following that, low risk patients should be seen every two-three years and all others should be seen annually. Educating the patient on worrying symptoms including fatigue, neuropathy, weight loss, night sweats, and bone pain is crucial to early detection of MGUS progression. Important tests to order at each visit are CBC, serum creatinine, serum calcium, serum protein electrophoresis, and serum free light chains. It is important to refer non-low risk patients to a hematologist and continue to reassess the patient's risk at every visit.

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