



REVIEW

The incidental monoclonal protein: Current approach to management of monoclonal gammopathy of undetermined significance (MGUS)

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ARTICLE INFO

Keywords:

Monoclonal gammopathy
Immunoglobulins
Smoldering multiple myeloma

SUMMARY

'Monoclonal gammopathy of undetermined significance' (MGUS) is a pre-malignant disorder characterized by limited clonal proliferation of the bone marrow plasma cells without any evidence of end-organ damage. A better understanding of the prevalence rates, natural history, and the risk factors for progression of MGUS, provides further insight into the clinical approach to management of this condition. The clinical implications of MGUS such as the risk of fracture, miscellaneous conditions associated with a monoclonal M-protein, and a practical approach to the management of MGUS patients based on a risk-stratification model are discussed in this review.

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Introduction

The incidental finding of a monoclonal protein (immunoglobulin) is encountered by physicians in a wide array of clinical practice settings. It is often discovered on a routine blood test in an outpatient setting, as an asymptomatic rise in serum total protein level and/or hypergammaglobulinemia. The next step is to identify if the hypergammaglobulinemia is due to a monoclonal (monoclonal gammopathy) or a polyclonal (polyclonal gammopathy) proliferation of immunoglobulin-secreting plasma cells. A polyclonal gammopathy usually reflects a heterogeneous group of non-hematologic diseases such as liver disease and connective tissue disorders,¹ whereas a monoclonal gammopathy is indicative of a hematologic disease process such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), Waldenström's macroglobulinemia (WM), AL amyloidosis or another monoclonal plasma cell disorder. The term "monoclonal gammopathy of undetermined significance" was first introduced in 1978 by Dr. Robert A. Kyle, and replaced previous terms such as "essential hyperglobulinemia" and "benign monoclonal gammopathy" after a study of 241 patients at the Mayo Clinic (Rochester, MN, USA) which highlighted the long-term risk and the malignant potential of this disorder.²

MGUS is an asymptomatic pre-malignant plasma cell proliferative disorder with a lifelong risk of progression to MM or another plasma cell dyscrasia.³ It is defined by the presence of a monoclonal M-protein less than 3 g/dl, less than 10% plasma cells in the

bone marrow if done, very low or no amount of urine monoclonal light chains (Bence Jones proteins) and the absence of CRAB features (hypercalcemia, renal failure, anemia, and lytic bone lesions) that can be directly attributed to the underlying monoclonal gammopathy.^{4–6} In the continuum of disease from MGUS to MM, is an intermediate pre-malignant asymptomatic phase termed 'smoldering multiple myeloma' (SMM). It is defined by an M-protein (IgG or IgA) of ≥ 3 g/dl and/or $\geq 10\%$ plasma cells in the bone marrow, without any end-organ damage (CRAB features absent).^{4–6} SMM is more advanced than MGUS and carries a significantly higher risk of progression; 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% per year for the next 10 years.⁷ MM is defined by $\geq 10\%$ plasma cells in the bone marrow, presence of serum and/or urine M-protein, and the presence of end-organ damage (CRAB features present) that can be attributed to the plasma cell proliferative disorder.^{4–6} This review will focus on MGUS – the most common monoclonal gammopathy (Fig. 1A and 1B).

Prevalence

The prevalence of MGUS increases with advancing age,^{8,9} and it is usually discovered in the elderly, with the median age at diagnosis around 70 years, with less than 2% patients under the age of 40 years.³ Some of the earlier studies from the United States¹⁰ and Europe^{11,12} had recognized a prevalence rate of approximately 1% and 3% for persons over the age of 50 and 70 years, respectively. In order to capture the true prevalence of MGUS within a specified time frame, a population-based study using sensitive laboratory techniques was performed on the residents of Olmsted County, Minnesota, where serum samples were obtained from 77% of the enumerated residents, 50 years or older.⁸ An agarose gel

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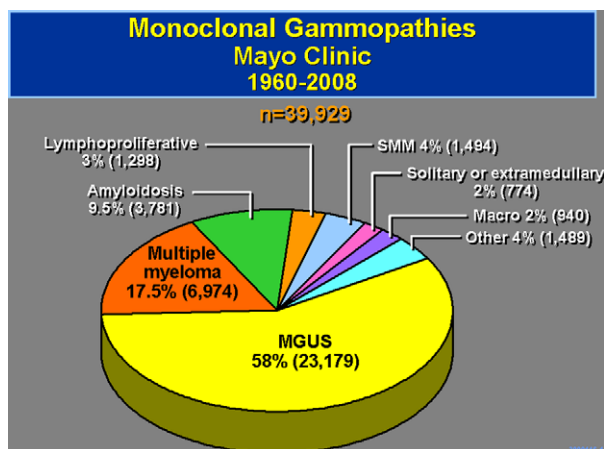


Fig. 1A. Monoclonal gammopathies diagnosed at the Mayo Clinic between 1960 and 2008. MGUS: monoclonal gammopathy of undetermined significance; Macro: macroglobulinemia; SMM: smoldering multiple myeloma.

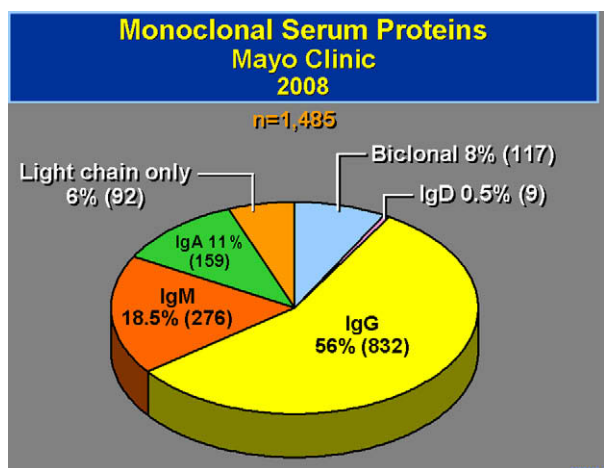


Fig. 1B. Type of monoclonal protein detected at the Mayo Clinic during 2008.

electrophoresis was performed on all the serum samples and those with a localized band or spike on electrophoresis were then subject to immunofixation for further analysis. MGUS was prevalent in 3.2% and 5.3% of persons over the age of 50 and 70 years, respectively. Of the persons in the study population whose race was known, 97.3% were whites. The age-adjusted rates were higher in men compared with women (4% versus 2.7%, respectively), a finding corroborated by other studies.^{9,11,13} An IgG immunoglobulin was most commonly found in 68.9% MGUS patients, whereas IgM, IgA and biclinal immunoglobulins were present in 17.2%, 10.8% and 3%, respectively. The serum light chain was kappa in 62% and lambda in 37.9%.

The prevalence of MGUS has been reported to be two–threefold higher in blacks compared with whites.^{14,15} In a study of 4 million African–American (AA) and white men admitted to Veterans' Affairs hospitals in the United States, the age-adjusted prevalence of MGUS was found to be threefold higher in AA compared with whites.¹⁴ In a community-based sample of the elderly, the prevalence of MGUS was more than twice as great in blacks (8.6%) than whites (3.8%).¹⁵ On the other hand, the prevalence of MGUS in a large Japanese population, exposed to low-dose radiation from the atomic bomb, has been found to be relatively lower compared with whites of Minnesota (2.4% versus 3.2%, respectively in persons older than 50 years).⁹ Since, the prevalence of MM is also two-fold in the blacks compared with whites, it supports the hypothesis

that the increased prevalence of MM in blacks is more likely due to an increased prevalence of MGUS in the black population, rather than a greater rate of MGUS transformation to MM.

Pathogenesis

The etiology of MGUS is unknown.^{16–18} However, the epidemiology of MGUS links to a complex pathogenic pathway characterized by the interplay of race related genetic predisposition and the environmental factors that influence it. In the first population-based study from Africa, the prevalence of MGUS in Ghanaian men was found to be twofold compared with whites of Minnesota, but was comparable to the AA population, thereby supporting the hypothesis that racial differences manifested in the genetic architecture are involved in the increased prevalence of MGUS among blacks.¹⁹ However, the stable prevalence between those 50 and 74 years old in the Ghanaian population has not been observed in the AA population. On the contrary, an increasing prevalence with age has been observed in the AA population, suggesting that environmental factors also play a role in the pathogenesis of MGUS.¹⁶ A familial occurrence and an increased risk in the first-degree relatives of patients with MGUS and MM has been reported, providing further evidence of shared genetic and environmental factors.^{20–24} In a study of 4 million US veterans, specific prior autoimmune, infectious and inflammatory conditions, but not allergic disorders, were associated with an elevated risk of MGUS and MM.²⁵ Interestingly, some studies have identified a personal history of pernicious anemia to be associated with an increased risk of MGUS and MM.^{22,25–28} In a recent series, the age-adjusted prevalence of MGUS was almost twofold higher among male pesticide applicators compared with the general population,²⁹ the risk was further increased with certain pesticide use.²⁹ Although chemicals, fertilizers, pesticides have all been linked to the development of MGUS and MM,¹⁶ their exact roles in the pathogenesis remains unclear and needs further investigation.

Monoclonal gammopathies are characterized by an idiotypic rearrangement of immunoglobulin genes which result in the production of an M-protein.³⁰ MGUS is characterized by a limited plasma cell proliferation resulting in the presence of less than 10% monoclonal plasma cells in the bone marrow, with a serum M-protein less than 3 g/dl. At least 5×10^9 plasma cells should be present to identify a monoclonal component (M spike) in serum protein electrophoresis.³¹ Usually, this large plasma cell clone will remain stable for many years without producing end-organ damage.^{17,32} However, at a constant rate of 1% per year, the abnormal plasma cell clone will escape the regulatory mechanisms and progress to a plasma cell neoplasm.^{3,32}

The cytogenetic changes that occur in MGUS (immunoglobulin translocations, aneuploidy, chromosome 13 abnormalities) bear a close resemblance to those observed in MM.^{33–38} The translocations involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32 occur due to errors in IgH switch recombination or somatic hypermutation. These are considered to be the primary genetic aberrations leading to the development of the abnormal plasma cell clone.^{31,37} Thus, the IgH translocation has a comparable prevalence in patients with MM and MGUS, occurring in approximately 60% and 46% patients with MM^{34,35} and MGUS,^{36,37} respectively. When IgH translocations are studied with interphase fluorescence in situ hybridization (FISH), the following pattern is noted: $t(11;14)$ is most commonly identified in 15–30% of MGUS, leading to the dysregulation of *cyclin D1* gene; $t(4;14)$ and $t(14;16)$ are recognized in a smaller subset of MGUS patients with subsequent dysregulation of *FGFR3/MMSET* and *C-maf* oncogenes, respectively.³¹ Both hyperdiploid and hypodiploid variants are found in MGUS and MM, although the former is more common

in both.³³ Hyperdiploid chromosomes are associated with approximately 40–50% of MGUS and occur usually in non-IgH translocated MGUS.^{33,38} The deletion of chromosome 13q, an adverse prognostic factor in MM, has been observed in approximately 50% MGUS patients,^{37,39} and occurs usually in hyperdiploid MGUS states.³³ On the other hand, deletion of chromosome 17p, which is associated with a shorter survival in MM, occurs rarely in MGUS.^{31,37,40–42}

Using flow cytometry, two distinct phenotypes of plasma cells have been identified in the MGUS bone marrow.^{43,44} The normal polyclonal plasma cells (low forward and side light scatter, CD38+, CD19+ and CD56–) and the clonal plasma cells (high forward and side scatter, CD38+, CD19– and CD56+) are present in both MGUS and MM, although the proportion of normal plasma cells is significantly higher in MGUS compared with MM.⁴⁴ In one study, 1.5% of MM patients had more than 3% normal plasma cells, whereas 98% of MGUS patients had more than 3% normal plasma cells.⁴⁴ Kumar et al. have observed that the ratio of CD45+ to CD45– plasma cells varies with the plasma cell proliferative disease stage, with a higher proportion of plasma cells expressing CD45 in the MGUS phase compared with MM.⁴⁵

The evolution of MGUS to MM or a related disorder is a multi-step process which is characterized by underlying genomic instability. However, the mechanisms that guide the sequence of events in transforming the 'stable' MGUS plasma cell clone into an 'unstable' malignant gammopathy still remain obscure. It is evident that alterations occur in both the plasma cell clone and the stromal component of the bone marrow microenvironment that propagates it. As in solid tumors, increased angiogenesis has been implicated in the proliferation of hematologic malignancies.^{46–48} In a study of 400 patients by Rajkumar et al. the micro-vessel density was found to progressively increase from MGUS to SMM to newly diagnosed MM, with the highest value associated with relapsed MM.⁴⁹ Other studies utilizing in vitro assays have also suggested a role of angiogenesis in the progression of MGUS to MM.^{50,51} In one study, a loss of angiogenesis inhibitory activity was found along the plasma cell disease spectrum, with 63% of MGUS samples inhibiting angiogenesis compared with only 4% of newly diagnosed MM cell samples.⁵⁰ Various cytokines have been linked to the malignant transformation of MGUS to MM. Interleukin (IL)-6 acts as an important paracrine growth factor in the pathogenesis of neoplastic plasma cells by inducing proliferation and inhibiting apoptosis.^{52–54} A significantly higher level of IL 6-receptor alpha-chain (CD126) is expressed in the neoplastic plasma cells in MGUS.⁵⁵ The production of IL-6 is stimulated from marrow stroma cells through various cytokines such as IL-1 beta,⁵⁶ tumor necrosis factor alpha,⁵⁷ and vascular endothelial growth factor (VEGF).⁵⁸ An important finding that needs further confirmation is the amplification of chromosome 1q21, observed in 0% of MGUS patients compared with over 40% of patients with MM and SMM, suggesting its role in disease progression.⁵⁹ While activating mutations of the *RAS* (*N* and *K RAS*) oncogenes occur rarely in MGUS, it is found commonly in MM.^{60–62} Since the risk of malignant transformation of MGUS is constant over time and is independent of its duration, it has been proposed that a second 'hit' is required for the clonal evolution of plasma cells, which may be different in IgH translocated versus non-IgH translocated MGUS. Other abnormalities associated with transition to symptomatic disease include p16 methylation, abnormalities in the *myc* family of oncogenes, secondary translocations and p53 mutations.⁵⁸

Risk factors for progression

The serum M-protein concentration at the time of MGUS diagnosis and the presence of IgA MGUS are two critical factors that

have been found to have prognostic significance across several studies.^{3,63–67} In a large population-based study involving 1384 subjects from southeastern Minnesota with a median follow up of 15.4 years, the risk of progression at 20 years was found to increase approximately twofold with every one g/dl increment in the initial serum M-protein value between 0.5 g/dl and 2.5 g/dl.³ A risk of 14%, 25% and 49% was observed for an initial M-protein value of 0.5 g/dl, 1.5 g/dl and 2.5 g/dl, respectively. However, the presence of monoclonal light chain in the urine did not predict progression.³ The patients with non-IgG (IgA and IgM) MGUS had an increased risk of progression compared to patients with an IgG monoclonal protein ($p = 0.001$).³ Similarly, a higher probability of malignant transformation has been observed in several studies with IgA^{3,63–66} and IgM^{3,65} variety of MGUS.

The bone marrow plasma cell (BMPC) content is also helpful for predicting progression. In a study involving 1104 patients with MGUS, greater than 5% marrow plasmacytosis was found to be an independent risk factor for evolution, with greater than 10% BMPC mass associated with an even higher risk, irrespective of the immunoglobulin class.⁶⁵ The BMPC percentage of 6–9% carries twice the risk of progression compared with marrow involvement that is 5% or less.⁶⁵ Similarly, when MGUS patients were divided based on BMPC percentage of less than 10% and between 10% and 30% (now termed SMM), the risk of malignant transformation was found in 6.8% and 37% of patients, respectively,⁶⁷ thereby justifying the 10% cut-off limit for BMPC in MGUS, and the recognition of SMM as a separate pre-malignant stage. On the other hand, Baldini et al. recognized a subset of IgG MGUS patients with a very low risk of evolution: serum M-protein <1.5 g/dl, BMPC <5%, no urine monoclonal light chain and no reduction in the level of uninvolved immunoglobulin.⁶⁷ The concomitant reduction in polyclonal or uninvolved immunoglobulins, a common occurrence in MM, has been associated with a higher risk of malignant transformation in some MGUS studies,^{65,67} but not in others.^{3,68,69}

Two studies have observed an initial abnormal free light chain (FLC) ratio as an important risk factor in the progression of patients with MGUS.^{70,71} Free light chains (kappa and lambda), that are not bound to the immunoglobulin, are secreted by the plasma cells of patients with MM (secretory, oligo-secretory and non-secretory) and light chain diseases like light chain multiple myeloma, AL amyloidosis, and light chain deposition disease (LCDD). The normal FLC ratio is 0.26–1.65 g/dl.⁷² A serum FLC ratio >1.65 and <0.26 indicates kappa and lambda light chain proliferation, respectively. An abnormal FLC ratio is suggestive of a monoclonal gammopathy, rather than polyclonal gammopathy or renal insufficiency.⁷² In a study of 1148 patients, the risk of progression to MM or another plasma cell proliferative disease with an abnormal serum FLC ratio was significantly higher compared with patients with a normal ratio at baseline (17% versus 5% at 10 years, and 35% versus 13% at 20 years, respectively) (hazard ratio 3.5, $p < 0.001$), and was independent of the size and type of M-protein.⁷¹

The presence of circulating plasma cells in the peripheral blood which are commonly detected in patients with active MM using a sensitive slide based immunofluorescent assay,⁷³ is also a risk factor for MGUS progression. In a study of 325 MGUS patients, 63 (19%) patients were found to have a median of 1% circulating plasma cells and were twice as likely to undergo progression to MM,⁷⁴ indicating a higher clonal proliferative rate in this particular subset.

A new model that incorporates 3 important risk factors was developed in order to risk stratify MGUS patients (Fig. 2). Patients with all 3 risk factors: non-IgG (IgA and IgM) MGUS, abnormal serum FLC ratio and serum M-protein value ≥ 1.5 g/dl have a 58% risk of progression at 20 years (high-risk), 37% with any 2 of these risk factors (high-intermediate risk), 21% with one risk factor (low-intermediate risk) and 5% when none of the risk factors are present

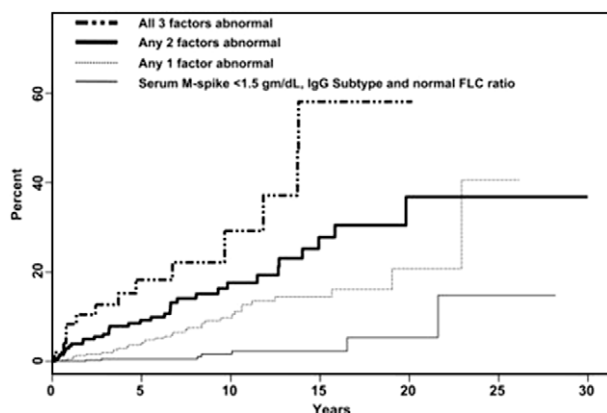


Fig. 2. Risk of progression of MGUS to myeloma or related disorder using a risk-stratification model that incorporates the FLC ratio and the size and type of the serum monoclonal protein. The top curve illustrates risk of progression with time in patients with all 3 risk factors, namely an abnormal serum kappa-lambda FLC ratio (<0.26 or >1.65), a high serum monoclonal protein level (≥ 1.5 mg/dl), and non-IgG MGUS; the second gives the risk of progression in patients with any 2 of these risk factors; the third curve illustrates the risk of progression with one of these risk factors; the bottom curve is the risk of progression for patients with none of the risk factors. (This figure was originally published by Rajkumar et al.⁷¹ © the American Society of Hematology).

(low risk).⁷¹ Recently, in a study by Rosiñol et al. the concept of “evolving” versus “non-evolving” MGUS has been introduced. An “evolving” MGUS has been defined as a progressively increasing pattern of the M-protein value, critically recognized in this study as the most important factor predicting malignant transformation. The progression rate at 10 years for the evolving and the non-evolving groups of MGUS were 55% versus 10%, corresponding rates at 20 years were 80% and 13%, respectively.⁶⁶ The authors of this study hypothesize that evolving MGUS is a form of an early MM, whereas non-evolving MGUS is the “true” stable MGUS which may or may not undergo malignant transformation.

Natural history

At the time of initial detection of M-protein, it is unclear if the plasma cells will proliferate substantially to cause end-organ damage (hypercalcemia, renal failure, anemia and lytic bone disease) requiring therapeutic intervention, or will remain stable without producing any symptoms. Hence the term “monoclonal gammopathy of undetermined significance” is appropriate at the time of initial diagnosis. It is important to understand the natural history of MGUS since it is relatively common in the general population over the age of 50, its prevalence increases with advancing age and the constant risk of 1% per year^{3,68} persists even after 25–30 years of diagnosis.^{3,68} Several studies from Mayo Clinic have been published on a group of 241 MGUS patients who were first identified between January 1956 and December 1970.^{2,68,69,75} These patients were followed up on a regular basis and their findings were periodically reported. In the last report of this series in 2004, only 16 of the 241 patients were alive.⁶⁸ After a median follow up of 13.7 years, a malignant plasma cell proliferative disease developed in 64 (27%) patients, 138 (57%) patients died from other causes without any evidence of symptomatic MM or a related disorder, 25 (10%) patients developed an increase in the level of M-protein which did not require therapy and 14 (6%) patients did not have an increase in the M-protein value. Among the cohort of patients that developed a plasma cell malignancy, 44 (69%) patients developed MM, including 10 patients who were diagnosed more than 20 years after the initial detection of M-protein. The main message from this report was that the risk of malignant

transformation persisted even after more than 30 years of follow up. The findings of this series were confirmed in a larger series which included 1384 MGUS patients with 11,009 person-years of follow up. An overall risk of approximately 1% per year was observed in the progression from MGUS to MM, lymphoma with an IgM M-protein, AL amyloidosis, and WM, which persisted even after long periods of stability.³ The cumulative probability of MGUS progression was 12%, 25% and 30% at 10, 20 and 25 years, respectively.³ The median M-protein value was 1.2 g/dl and the median BMPC content was 3%. In another study of 434 patients with a median follow up of 5.2 years, the risk of progression was found to be 15.4% and 34% at 10 and 20 years, respectively.^{76,77} The median M-protein value was 1.56 g/dl and the median BMPC content was 4.6%.

The difference in the rate of progression in the two studies can be attributed to the difference in the plasma cell burden, which is a measure of serum M-protein size and BMPC percentage (1.2 g/dl and 3% versus 1.56 g/dl and 4.6%, respectively).^{3,76,77} A similar elevated risk of progression (17% at 10 years) has also been reported in the Mayo Clinic series of 241 patients with a median M-protein value of 1.7 g/dl.⁶⁹ However, these actuarial rates can seldom be used independently in clinical practice as the MGUS population is generally older with multiple comorbid conditions. Therefore, the risk of death at 10 years for MGUS patients is 6% from plasma cell cancer versus 53% from other diseases.³ Similarly, when competing causes of death are taken into account, the rate of progression at 25 years of follow up is significantly lower at 11.2%.⁷¹ Thus, an important point to realize is that the majority (approximately 75–90%)^{3,68} of MGUS patients will not progress to MM or another monoclonal plasma cell disorder in their lifetime, and will usually die from a non-plasma cell related disease process.

Clinical implications

An increased osteoclastic bone resorption and impaired osteoblastic bone formation is observed in MM resulting in osteolytic bone lesions, osteopenia, pathologic fractures and hypercalcemia. An altered balance between the receptor activator of nuclear factor kappa-B ligand (RANKL) and its decoy receptor osteoprotegerin (OPG), leads to osteoclastogenesis resulting in excessive bone resorption. An increase in RANKL/OPG ratio has been observed in MM⁷⁸ and MGUS.⁷⁹ The increased RANKL/OPG ratio, macrophage inflammatory protein (MIP)-1alpha, interleukin (IL)-3 and interleukin (IL)-6 have been implicated in potentiating the osteoclast activity. Interleukin (IL)-1 beta produced by plasma cells, has potent osteoclast activating factor activity and can induce paracrine IL-6 production.^{56,80} On the other hand, the increased activity of IL-3, IL-7 and DKK1, produced by marrow stroma, inhibits osteoblast differentiation and thereby affects bone formation.⁸¹

Studies to evaluate the skeletal turnover, utilizing serum and/or urine bone remodeling markers have found that MGUS patients display a higher value of these markers compared to the healthy population, but lower than those in MM, signifying increased bone turnover in MGUS.^{82–86} However, the histomorphometric study of bone biopsy found bone remodeling to be normal in 29 MGUS patients,⁸⁷ while normal levels of the biochemical markers of bone resorption and formation were found in 18 MGUS patients.⁸⁸ It has been proposed that increased osteoclastogenesis leading to increased bone resorption is present in MGUS but may be compensated by normal bone formation, unlike in patients with MM.⁷⁹ Since these studies yielded mixed results, they were unable to clarify the risk of fracture in MGUS.

To address this issue, Melton III et al. conducted a population-based retrospective cohort study on 488 Olmsted County, Minnesota residents with MGUS.⁸⁹ The median age of residents was

Table 1

Other diseases which may be associated with an M-protein.

Miscellaneous conditions	Description	References
POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes)	A rare paraneoplastic syndrome secondary to a plasma cell disorder. Presence of a monoclonal plasma cell disorder (almost always lambda light chain type), peripheral neuropathy and 1 major criterion (sclerotic bone lesions, Castleman disease, VEGF elevation) and 1 minor criterion [organomegaly, extravascular volume overload, endocrinopathy (most commonly hypogonadism, excluding diabetes mellitus or hypothyroidism), skin changes, papilledema, thrombocytosis/polycythemia]. The features should have a temporal relationship to each other and no other attributable cause. Plasma and serum levels of VEGF are markedly elevated and correlate with the disease activity; thrombocytosis is common. Median survival 13.8 years in one report.	[6,18,100,101]
Skin disease	Scleromyxedema (Papular mucinosis, Lichen myxedematosus) is a rare skin disorder associated with an IgG lambda paraprotein. Other associated conditions are pyoderma gangrenosum, necrobiotic xanthogranuloma and erythema elevatum diutinum. Schnitzler syndrome is characterized by chronic urticaria and IgM M-protein.	[102–107]
Immune suppression	Post-transplant in patients undergoing kidney, liver, heart and autologous bone marrow transplant; acquired immune deficiency syndrome (AIDS). The M-protein is transient and disappears with the recovery of the immune system.	[108,109]
Neurologic disorder	Sensorimotor peripheral neuropathy of unknown cause (IgM). Differential diagnosis includes peripheral neuropathy associated with AL amyloidosis and POEMS syndrome.	[104,110]
Renal disorders	Idiopathic focal segmental glomerulosclerosis and monoclonal gammopathy with fibrillary deposits.	[111–114]
Infections	Contradictory reports from two studies on the association of <i>Helicobacter Pylori</i> with MGUS. No clear evidence of an association yet.	[115,116]
Hematologic disorders	Malignant lymphoma (IgM) and CLL (IgG).	[117–119]
Connective tissue disorders	Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyalgia rheumatica and ankylosing spondylitis; however the supporting evidence is weak.	[120–123]
Others	Hepatitis C virus positive cryoglobulinemia, acquired C1 inhibitor deficiency, capillary leak syndrome, acquired von Willebrand's syndrome, and acquired angioedema type 2.	[124–128]

73.3 years and they were followed for 3901 person-years. The incidence of fracture was found in 200 patients resulting in 385 fractures. The risk of vertebral fractures was significantly elevated [standardized incidence ratio (SIR), 6.3; 95% confidence interval (CI), 5.2–7.5]; while the risk of hip fractures was partially elevated (SIR, 1.6; 95% CI, 1.2–2.2). Cumulatively, the study reported a 2.7-fold increased risk of axial fractures compared to the peripheral limb fractures.⁸⁹ In patients with a fracture, those with IgG MGUS and lambda light chain reported a relatively lower risk of fractures compared to non-IgG (IgA and IgM) MGUS and kappa light chain, respectively. In another study by Gregersen et al. 187 fractures were identified during 9754 person-years of follow up in 1535 MGUS patients, yielding a relative risk of 1.4;⁸⁴ substantially lower than what was reported by Melton et al. However both studies identified patients with a kappa light chain type of monoclonal protein at an increased risk for fracture.^{84,89} Other studies have also identified an increased risk of axial fractures in MGUS patients,^{84,89–91} with the highest risk observed in patients with a reduced lumbar bone marrow density.⁹⁰

Vertebral fractures, either symptomatic or asymptomatic, are associated with a future risk of other vertebral and non-vertebral fractures and have a direct impact on mortality.⁹² In a cohort of 134 patients presenting with back pain and MRI evidence of acute osteoporotic vertebral fracture, almost 15% were found to have MGUS.⁹¹ The RANKL/OPG ratio has been found to be elevated in patients with a vertebral fracture compared to patients without a vertebral fracture.⁹⁰ Bisphosphonate therapy, which is known to be effective in bone disease related to MM and other cancers, may also improve the bone density in patients with osteopenia or osteoporosis related to MGUS.^{93,94} However, the cost, and the adverse effects of prolonged bisphosphonate use such as jaw osteonecrosis,⁹⁵ should be considered while patients receive this therapy.

There are 3 studies that indicate a slightly increased risk of venous thromboembolic disease (VTD) in MGUS compared with the general population.^{96–98} Two of these studies identified IgG MGUS to have a lower risk compared with non-IgG MGUS patients.^{96,97} In a series of 310 MGUS patients, 6.1% developed a VTD during a

mean follow up of 44 months.⁹⁸ In another study, 7.5% of MGUS patients developed a VTD at a median of 4 months after diagnosis.⁹⁷ An increase in the level of factor VIII and von Willebrand's factor have been implicated as the prothrombotic abnormality leading to the increased risk of VTD⁹⁹ but further studies are needed to investigate this.

The presence of an M-protein usually signifies a hematologic disease process such as MGUS, MM, AL, WM or another monoclonal plasma cell disease. Once these diseases have been excluded by clinical exam and laboratory tests, further evaluation should focus on disorders which are occasionally associated with a monoclonal protein (Table 1).

Management

At present, MGUS patients do not require any form of therapy, only regular lifelong follow up is necessary (Fig. 3).

The IgG and IgA MGUS may progress to MM, AL amyloidosis or another plasma cell proliferative disease; in contrast, the IgM MGUS may progress to lymphoma or WM. IgD MGUS is rare and the presence of IgD M-protein almost always indicates MM or AL amyloidosis.¹⁸ A bone marrow aspirate and biopsy should be performed with any one of the following risk factors: M-protein ≥ 1.5 g/dl, IgA or IgM M-protein, abnormal FLC ratio or a clinical suspicion of malignant plasma cell disorder. A baseline dual energy X-ray absorptiometry (DEXA) scan and/or MRI should also be considered in MGUS patients. Based on the risk-stratification model, most of the MGUS patients can be categorized as low risk and low-intermediate risk, with a smaller group who are considered high-risk patients. Patients with a low risk (M-protein <1.5 g/dl, IgG M-protein and normal FLC ratio) constitute nearly 40% of the newly diagnosed MGUS and should be followed at 6 months and every 2–3 years thereafter, as their actuarial and real probability of malignant transformation at 20 years is 5% and 2%, respectively.⁷¹ All the other subgroup of patients (low-intermediate, high-intermediate and high-risk) should be rechecked in 6 months

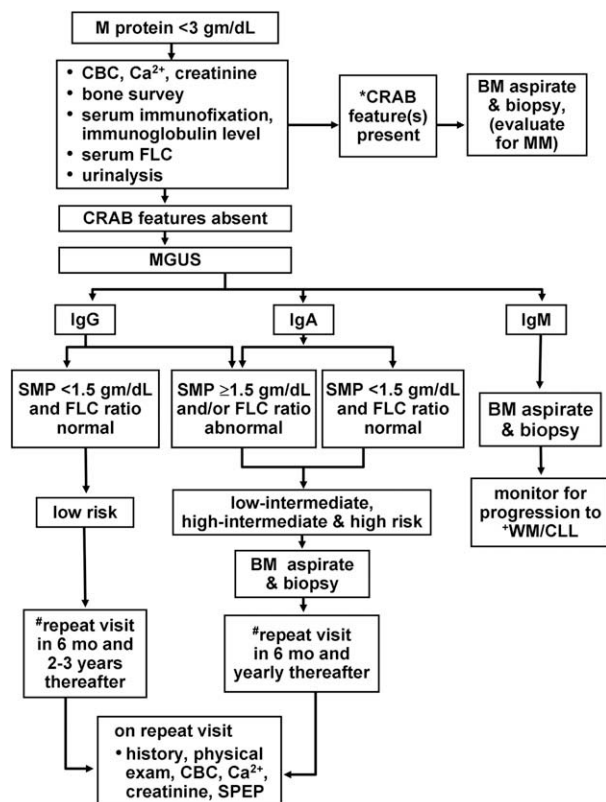


Fig. 3. Management of patients with M-protein <3 g/dl (excluding patients with AL amyloidosis, Waldenström's macroglobulinemia (WM) or other diseases which may be occasionally associated with an M-protein as listed in Table 1). *CRAB (hypercalcemia, renal failure, anemia, lytic bone lesions). *Repeat visits at more frequent intervals if M-protein value is progressively increasing. *WM (Waldenström's macroglobulinemia), CLL (chronic lymphocytic leukemia), MGUS (monoclonal gammopathy of undetermined significance), MM (multiple myeloma), BM (bone marrow), FLC (serum free light chain), SMP (serum monoclonal protein), SPEP (serum protein electrophoresis).

and then yearly thereafter. Although MGUS patients are more likely to die from non-plasma cell diseases, it is imperative to identify individuals where the MGUS clone is more likely to develop into MM which is an incurable malignancy. Patients with a high-risk (M-protein ≥ 1.5 g/dl, non-IgG M-protein and abnormal FLC ratio) constitute a smaller number but have a significantly higher rate of malignant transformation at 20 years – actuarial and real probability of 58% and 27%, respectively.⁷¹

On return visits for all MGUS patients, a thorough history, physical exam, complete blood count, serum calcium and creatinine, and serum protein electrophoresis should be obtained. Further testing should be determined by the individual symptoms. A pattern of rising M-protein value should be followed closely with more frequent follow up visits before these patients develop a symptomatic disease.⁶⁶ On the other hand, the spontaneous resolution of an M-protein without an apparent cause or treatment of the underlying disorder is rare.³ A clinical therapeutic trial can be undertaken for the high-intermediate/high-risk MGUS patients when more information is obtained on the molecular basis of formation and transformation of the MGUS clone, and specific non-toxic drugs are available for intervention.

Practice points

- A monoclonal gammopathy indicates a hematologic disease process whereas a polyclonal gammopathy is usually associated with liver or connective tissue diseases.

- 'Monoclonal gammopathy of undetermined significance' (MGUS) has been observed in more than 3% of the general population, 50 years or older, in a population-based study. It carries a lifelong constant risk of 1% per year progression to MM or a related monoclonal plasma cell disorder. Smoldering multiple myeloma (SMM) is a more advanced pre-malignant disease stage that progresses to multiple myeloma (MM) at 10% per year for the first 5 years, approximately 3% per year for the next 5 years and 1% per year for the next 10 years.
- The prevalence of MGUS is more than twofold higher in African Americans compared with the Caucasians, and is higher in men than in women. The epidemiology of MGUS suggests an interplay of race related genetic predisposition with the environmental factors that influence it.
- The underlying mechanisms of formation and transformation of the MGUS clone are not completely understood. The translocation involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32 could be the early genetic anomaly that leads to the formation of the abnormal MGUS clone in IgH translocated MGUS; hyperdiploidy commonly occurs with non-IgH translocated MGUS. Increased angiogenesis and cytokines (IL-6, IL-1) have been implicated in MGUS progression.
- Three adverse risk factors (non-IgG MGUS, abnormal serum FLC ratio and serum M-protein ≥ 1.5 g/dl) are used to risk stratify MGUS patients. At 20 years of follow up, patients with all 3 risk factors have a 58% risk of progression, 37% with any 2 risk factors, 21% with one risk factor and 5% when none of the risk factors are present (low risk). Patients with low risk constitute nearly 40% of MGUS patients.
- The actuarial and the real (accounting for competing causes of death) probability of MGUS progression is 30% and 11% at 25 years of follow up, respectively; approximately 75–90% of MGUS patients will not progress to MM or a related monoclonal plasma cell disorder.
- At present, MGUS patients do not require any form of therapy, only regular lifelong follow up is indicated before serious complications of MM such as renal failure, hypercalcemia and lytic bone lesions occur.

Research agenda

The molecular basis of formation and transformation of the MGUS clone needs better understanding.

A consensus is needed to develop effective follow up guidelines based on important risk factors of progression from MGUS to MM.

A clinical trial may be considered for the high-intermediate/high-risk MGUS patients with relatively non-toxic drugs to prevent or delay their progression to MM or another monoclonal gammopathy.

Conflict of interest statement

None declared.

Acknowledgements

We thank Dr. Shaji Kumar for his contribution in the critical review of the manuscript. We sincerely appreciate the support of our colleagues and mentors (Division of Hematology, Mayo Clinic, Rochester, MN) in the preparation of this manuscript.

Supported in part by research grant CA 62242 from the National Cancer Institute.

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