

SPOTLIGHT REVIEW

Pathogenesis and progression of monoclonal gammopathy of undetermined significance

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In Caucasians, monoclonal gammopathy of undetermined significance (MGUS) is an age-related condition with prevalence as high as 3% in persons older than 50 years. Compared with whites, blacks have around two- and threefold higher prevalence rates of MGUS and multiple myeloma (MM), respectively. Risk of progression from MGUS to MM has been found to be very similar in whites and blacks. On average, the transformation rate to a malignant monoclonal gammopathy is 1% per year, with the mechanisms of progression likely related to bone marrow microenvironment and/or the cytokine network. Overall, the actuarial probability of progression at 25 years of follow-up is about 30%. However, when the competing causes of death are taken into account, the actual rate of progression is only 11%. The predictors of malignant transformation are the plasma cell mass (M-protein size and/or proportion of plasma cell in the bone marrow), IgA isotype, serum free light-chain ratio and 'evolving' type and ratio between phenotypically aberrant and normal bone marrow plasma cells. It is recommended to follow these patients, particularly those with high risk of progression, annually to detect MM before complications, such as renal failure or extensive skeletal, involvement occur.

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Concept

The term monoclonal gammopathy of undetermined significance (MGUS) indicates the presence of a monoclonal protein (M-protein) in individuals with no features of multiple myeloma (MM), Waldenström's macroglobulinemia, primary amyloidosis or other related disorders.¹ Patients with MGUS have a serum M-protein size lower than 3 g per 100 ml, and proportion of bone marrow plasma cells of less than 10%, with no clinical manifestations related to their monoclonal gammopathy (Table 1).^{1,2} MGUS was initially considered to be a benign condition and was frequently named 'benign' or 'idiopathic' monoclonal gammopathy.^{3,4} However, from the time of the pioneer observations in the Mayo Clinic (Rochester, MN, USA) series, this disorder could no longer be considered as 'benign' as a number of patients ultimately develop a malignant monoclonal gammopathy.^{1,5–8} For this reason, Dr Robert Kyle coined the term 'monoclonal gammopathy of undetermined significance'.^{1,5} Considering that MGUS is usually an unexpected

finding in a routine medical survey, or in the study of an unrelated disorder, not surprisingly, this condition is usually first seen by physicians working in many different fields of medical practice. In consequence, it is crucial to know the significance of the finding: whether it will require further investigation and whether it will remain stable or, by the contrary, will evolve into a symptomatic monoclonal gammopathy requiring therapeutic intervention.⁹

Epidemiology

Prior studies based on Caucasians showed that the prevalence of MGUS increases with age. For many years, it was considered that the prevalence of MGUS was 1 and 3 % in persons older than 50 and 70 years, respectively.^{10–14} However, in a recent study performed on residents of Olmsted County (MN, USA), the prevalence of MGUS has been found to be even higher than what was previously reported (that is, 3.2 and 5.3% in persons older than 50 and 70 years, respectively). The median age at diagnosis is around 70 years and less than 2% patients with MGUS are under the age of 40 years.¹⁵ The prevalence of MGUS is higher in men than in women (that is, 4 versus 2.7% among persons older than 50 years). In a series from the United States, the prevalence of MGUS was higher in blacks than in whites.¹⁶ In a large population-based screening study from Ghana, the prevalence of MGUS increased by twofold when compared with that of a white population from Minnesota.¹⁷ These two latter studies identify a similar prevalence of MGUS in patients from Africa as well as in Americans of African origin, and confirm ethnic differences in the prevalence of MGUS.^{16,17} Interestingly, in the study from Ghana, the prevalence of MGUS was similar in patients aged 50–54 years (5.33%) and 70–74 years (5.38%).¹⁷ This is in contrast with the prevalence observed in the Minnesota population aged 50–54 years (1.83%) and 70–74 years (5.12%).¹⁵ The reasons for this difference are unclear. Finally, in a large Japanese population of atomic bomb survivors, older than 50 years, in Nagasaki, the prevalence of MGUS was 2.4%, that is, substantially lower than the 3.2% observed in the Minnesota population.¹⁸ This is consistent with the lower incidence of monoclonal gammopathies in the Asian population and the fact that radiation exposure does not increase the prevalence of MGUS. In a recent study, based on a large population from Olmsted County, the median duration of MGUS prior to its recognition was found to be 11 years.¹⁹

Pathogenesis

Genesis

The etiological risk factors for MGUS and MM are unknown.^{20–22} However, there are data to support the operation of genetic factors. Thus, Scandinavian population-based studies have

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Table 1 Diagnostic criteria of monoclonal gammopathy of undetermined significance

- Serum M-protein size <3 g per 100 ml
- Bone marrow plasma cells <10%
- No clinical manifestations or other laboratory abnormalities attributable to monoclonal gammopathy

shown evidence of familial aggregation for MGUS and MM,²³ and there have been several smaller studies as well.^{24–27} Also, the observed two- and threefold increased risk of MGUS and MM in blacks compared with whites supports the hypothesis of a race-related predisposition.²⁸ Probably, the elevated risk of MGUS in blacks also reflects unknown environmental influences, which possibly interact with genetic factors. Recently, a nationwide study based on 4 million US veterans found immune-related conditions to be associated with the elevated risk of MGUS and MM.²⁹ Similar findings, based on the Scandinavian data, have also been reported.^{23,30} From all the above, it is clear that further studies are needed to better define the role of genetics and environmental factors in the development of monoclonal gammopathies. It is of interest that there are transient monoclonal gammopathies as a result of a temporary immunodeficiency in acquired immunodeficiency syndrome as well as in organ transplantation (bone marrow, kidney, liver). In this situation, monoclonal gammopathy disappears with the recovery of the immune system.⁹ In contrast, the disappearance of an M-protein without a known cause or a therapeutic intervention is exceedingly rare.²²

Monoclonal gammopathies are characterized by a rearrangement of immunoglobulin genes, which results in the production of an idiotypic monoclonal protein.^{9,21,22} It is important to keep in mind that for a plasma cell clone to produce a recognizable M-spike at serum or urine electrophoresis, the plasma cell clone must be quite large. In MGUS, this large plasma cell clone usually remains stable for many years with no increase in the M-protein size. However, on average, in approximately 1% patients per year the plasma cell clone evolves into a symptomatic monoclonal gammopathy.³¹ In these patients, who develop a malignant plasma cell condition, the MGUS state constitutes a pre-malignant phase and the progression occurs when the plasma cell clone escapes the regulatory mechanisms that were limiting the tumor growth for years.^{9,21} It has been suggested that one or more oncogenic steps promote genomic instability, resulting in MGUS.^{32,33} In fact, about 50% patients with MGUS have primary immunoglobulin heavy chain (IgH) translocations and it is likely that in these patients translocations involving immunoglobulin genes constitute the initial immortalizing event.³⁴ On the other hand, it is of interest that almost all the genetic changes observed in patients with MM (that is, aneuploidy, chromosome 13q deletion or even translocation t(4;14)) are already present in many patients with MGUS.^{34,35} In a recent report, patients with MGUS and MM had a high and similar frequency of hyperdiploidy, whereas hypodiploidy was rarely observed in MGUS. Interestingly, chromosome 13q deletion was almost always observed only in hyperdiploid MGUS.³⁵ Furthermore, the clonal plasma cells in patients with MGUS have a phenotypic profile similar to the one observed in the myelomatous plasma cells (CD38+, CD56+ and CD19–), although the proportion of phenotypically normal plasma cells is higher in patients with MGUS than in those with MM.³⁶ In fact, there are two populations of plasma cells in individuals with MGUS, one normal or polyclonal (CD38+, CD56– and CD19+) and the other clonal with an abnormal phenotype

(CD38+, CD56+, CD19–). In one study, the proportion of bone marrow polyclonal plasma cells, assessed by four monoclonal antibodies (CD38 or CD138, CD56, CD19 and CD45), was the best single factor to distinguish MGUS from MM.³⁶ Thus, in this study, less than 2% patients with MM had more than 3% normal plasma cells, whereas 98% patients with MGUS had more than 3% normal plasma cells.³⁶ It has recently been shown that CD117 (c-kit) is aberrantly expressed in about 50% individuals with MGUS and also in about one-third of patients with MM, who have an unexpected good prognosis.³⁷ Bataille *et al.*³⁷ have raised the question on whether the subset of c-kit-positive MM with a good outcome could come from CD117+ MGUS. Finally, gene expression profiling (GEP) using a first generation microarray showed that normal plasma cells could be distinguished from plasma cells of MGUS and MM, but plasma cells from MGUS and MM were indistinguishable.^{38,39} More recently, applying more sophisticated data to a larger number of samples and by using a third-generation microarray, an MGUS signature different from the GEP pattern observed in MM was identified.⁴⁰ Moreover, patients with MM showing an MGUS-like molecular GEP signature had a significantly longer survival despite a lower complete remission rate. This could be due to the re-establishment of an MGUS state after treatment.⁴⁰ However, a concern about this study is the issue of a possible contamination with nonmalignant cells, a fact that frequently occurs in situations in which the bone marrow involvement by plasma cells is low, such as in MGUS.⁴¹ In this regard, in a recent re-analysis of the same data set, where contamination with nonmalignant cells was carefully excluded, the same pattern could not be reproduced.⁴¹ Consequently, the existence of MGUS-like MM as an entity is still being questioned.⁴¹ In any event, the finding of a possible better survival for patients with the MGUS-like signature is of conceptual and practical interest and deserves further investigation with refined methodology. Keeping in mind that the genetic aberrations observed in MGUS are similar to those observed in MM and that the clonal plasma cells in MGUS display a similar phenotypic profile to myelomatous plasma cells, it is very likely that the plasma cell clone is already 'malignant' from the time it appears.

Mechanisms of progression

Once the MGUS clone is established, the molecular basis of its progression to a malignant monoclonal gammopathy remains poorly understood.^{9,20,21} In fact, it is currently believed that the above-mentioned genetic aberrations observed in MGUS are early events necessary for the immortalization of the clone but insufficient for promoting the progression to a malignant monoclonal gammopathy. In this sense, there is growing evidence that the stromal component of the bone marrow microenvironment (that is, non-tumorous cells providing growth and survival factors) plays an important role in the development of monoclonal gammopathies.⁴² In support of this, it has been shown that bone marrow angiogenesis significantly increases in the advanced stages of monoclonal gammopathies from MGUS to symptomatic MM.^{43,44} This suggests that angiogenesis might be related to MGUS progression. In fact, it has been considered that MGUS is the avascular phase of MM.⁴⁴ Unfortunately, serial follow-up studies to investigate whether an increase in angiogenesis is a determinant factor for the progression from MGUS to MM have not yet been carried out. Furthermore, it has been hypothesized that the dysregulation of various cytokines might be involved in the transition from MGUS to MM. Thus, it has been suggested that interleukin (IL)-1 β could play a role in the MGUS transformation as well as in the development of

skeletal disease.⁴⁵ IL-6 and tumor necrosis factor- α have also been considered to be involved in the pathogenesis of monoclonal gammopathies.^{46,47} However, in our experience, an increase in the serum levels of these two cytokines was not associated with a higher probability of malignant evolution.⁴⁸

What limits plasma cell growth and maintains a long-lasting MGUS state is uncertain. It seems that a second 'hit' is necessary to activate the mechanisms to promote plasma cell growth, with the malignant transformation being a matter of plasma cell quantity and time. In addition, there is recent evidence supporting a role for immune-mediated conditions in the etiology/progression of MGUS and MM.^{23,29,30,49} In the case of the so-called 'evolving' MGUS (see the section 'Predictors of malignant transformation'), the mechanisms that limit the growth of the emerging plasma cell clone would not exist and, irrespective of the initial plasma cell mass, all these patients would eventually end up with a symptomatic monoclonal gammopathy. In fact, the authors of this review believe that evolving MGUS are slowly growing myelomas from the beginning, but this observation needs confirmation in other series. There is no doubt that the genomics era with GEP and proteomics will help in delineating the mechanisms that promote plasma cell growth and proliferation, enhancing the understanding of the pathogenesis of the disease.^{40–42,50} Hopefully, this will result in the identification of novel molecular targets able to predict the progression of MGUS to a clinically overt disease and perhaps it will be helpful in the development of novel targeting therapies for patients at high risk of progression, particularly those with the evolving types.

Evaluation and differential diagnosis

Monoclonal gammopathy of undetermined significance is generally diagnosed after a routine blood test reveals a homogeneous spike at serum protein electrophoresis. When discovered during the evaluation of a medical problem, MGUS is generally an unrelated, incidental finding. Patients with MGUS have a serum M-protein size lower than 3 g per 100 ml and less than 10% bone marrow plasma cells, and are asymptomatic from their monoclonal gammopathy with no bone pain, anemia-related symptoms, hypercalcemia, renal failure, recurrent bacterial infections or extramedullary plasmacytomas (Table 1). The physical examination is normal when the monoclonal gammopathy is due to MGUS.

With regard to the diagnostic tests, serum protein electrophoresis is the most common method to detect and quantify a monoclonal protein. The 24 h urine protein excretion and urine electrophoresis allow quantitation of the M-protein in the urine. The immunofixation of serum and urine is necessary for the identification of the immunoglobulin class and the light-chain type. A bone marrow aspirate and a skeletal survey are generally performed to rule out myeloma. However, when the likelihood of myeloma is very low (that is, a low serum M-spike, less than 1.5 g per 100 ml; no significant light-chain proteinuria; and normal hemoglobin, creatinine and calcium), the bone marrow aspirate and the skeletal survey are not considered necessary.^{9,21}

A serum M-spike higher than 3 g per 100 ml, or a urine light-chain protein greater than 1 g/24 h, and/or a proportion of bone marrow plasma cells of 10% or greater are consistent with MM. Patients who fulfill the diagnostic criteria of MM, but are asymptomatic, are considered to have 'smoldering multiple myeloma' (SMM) (Table 2).² Patients with an M-spike in serum and/or urine and organ damage (skeletal involvement, anemia, hypercalcemia, renal function impairment, recurrent

Table 2 Diagnostic criteria of smoldering multiple myeloma

- Serum M-protein size ≥ 3 g per 100 ml and/or Bone marrow plasma cells $\geq 10\%$
- No clinical manifestations or other laboratory abnormalities due to monoclonal gammopathy

bacterial infections and/or soft-tissue plasmacytomas) have symptomatic MM.²

In patients with a serum M-protein size lower than 3 g per 100 ml, no urine light-chain protein excretion and less than 10% bone marrow plasma cells, the presence of anemia or renal insufficiency is more likely due to an associated disease than due to the monoclonal gammopathy. On the other hand, in a patient with constitutional symptoms, lytic bone lesions, a discrete serum M-spike and less than 10% bone marrow plasma cells, the most likely diagnosis is a metastatic carcinoma with coincidental MGUS. If the M-protein and the proportion of plasma cells in the bone marrow are consistent with MGUS but there is a nephrotic syndrome, congestive heart failure, peripheral neuropathy, orthostatic hypotension, massive hepatomegaly or any combination of these, the most likely diagnosis is primary systemic amyloidosis AL, and less likely is light-chain deposition disease resulting from the deposition of light chain in tissues and organs.^{9,21,22} If there is peripheral neuropathy, organomegaly, endocrinopathy, skin changes and osteosclerotic lesions, the most likely diagnosis is POEMS syndrome, particularly if there is a lambda light-chain isotype and increased vascular endothelial growth factor serum levels.⁵¹ An exceedingly rare syndrome associated with a monoclonal gammopathy, usually of IgG-lambda type, is scleromyxedema.⁵²

Malignant transformation in MGUS

A number of observational studies focused on both the progression rate and the predictors of malignant transformation in patients with MGUS have been published. The results of these studies are summarized below.

Risk of malignant transformation

The first study on the outcome of individuals with MGUS was performed at the Mayo Clinic.¹ The seminal series including 241 patients diagnosed with MGUS between 1956 and 1970 has been carefully updated and periodically reported during the last 25 years, showing the natural history of this condition.^{1,5–7} From the first reports of this study, it became evident that MGUS could no longer be considered as benign. Thus, in the last report, when all but 16 patients of the series had died, the actuarial probabilities of malignant transformation were 17, 34 and 39% at 10, 20 and 25 years of follow-up, respectively, with an annual transformation rate of 1.5%.⁷ Of note, in this series, the risk of progression was indefinite, persisting even after further 30 years of follow-up.

Aside from this pioneer series, the risk of malignant transformation in MGUS has been investigated in a number of studies. One concern in this type of analysis could be its reproducibility, as the results may vary from series to series, mainly due to the possible bias resulting from the number of patients, the different follow-up duration or selective referral.³¹ However, it is of note that a similar risk of transformation has been observed in all studies with long-term follow-up.^{7,31,53–58}

Table 3 shows that, on average, the probability of malignant transformation at 10 years ranges from 12 to 17% and from 25 to 34% at 20 years.^{7,31,54,56,57} However, the actuarial probability is clinically relevant only if patients do not die from other causes before the malignant transformation occurs. This is particularly important in conditions presenting at an advanced age, such as MGUS. In a large Mayo Clinic series, the actual rate of progression at 25 years of follow-up, when the competing causes of death were taken into account, was 11.2%.³¹ The rate of progression is not influenced by age,²³ although the cumulative risk of progression during a patient's lifetime is higher in younger individuals.

Predictors of malignant transformation

The results reported in the more durable studies on the factors associated with malignant evolution of MGUS are summarized in Table 4.^{7,31,53–59} No reliable predictors of progression were found in the first Mayo Clinic series⁷ and in the studies with relatively small number of patients.^{7,56} However, in the series including a larger number of cases, three features emerged as important predictors of progression: (a) the serum M-protein size, (b) the extent of bone marrow involvement by plasma cells and (c) the IgA M-protein isotype (Table 4). Concerning the impact of the M-protein concentration on MGUS progression in the largest series with longest follow-up reported so far, the risk of progression at 20 years progressively increased from 14, 25, 41 and 49% for a monoclonal protein higher than 0.5, 1.5, 2.0 and 2.5 g per 100 ml, respectively.³¹ With respect to the proportion of bone marrow plasma cells, in the three studies in which a bone marrow aspirate was done at diagnosis, the extent of bone marrow involvement was significantly associated with a higher risk of malignant transformation.^{54,55,57} In all these three studies, the proportion of bone marrow plasma cells was estimated independently by two experienced examiners and the

plasma cell percentages were estimated from 300 to 500 cell-count by each observer. It is also of interest that in almost all series the IgA M-protein type has been associated with a higher risk of malignant transformation. In line with the above findings, Baldini *et al.*⁵⁷ identified a subgroup of patients at a very low risk of progression: IgG type with a serum M-protein value lower than 1.5 g per 100 ml, a proportion of bone marrow plasma cells lower than 5% with no urine light chain protein excretion and no reduction in the level of uninvolved immunoglobulins.

More recently, the serum free light-chain ratio (that is, the ratio of free kappa to free lambda chains) has been shown to be an independent predictor of malignant transformation in MGUS.⁶⁰ The normal free light-chain ratio is 0.26–1.65 and an abnormal ratio is considered a marker of clonal expansion. A ratio below 0.26 indicates an excess of lambda chains, whereas a ratio above 1.65 is indicative of an excess of kappa chains production. In the Mayo Clinic experience, the free light-chain ratio was an independent predictor for malignant transformation that helped the investigators to recognize patients with high and low risk. Patients with an abnormal serum free light-chain ratio, non-IgG monoclonal protein and an M-protein size higher than 1.5 g per 100 ml had an actuarial risk of progression of 58% at 20 years (high-risk MGUS) as compared with a 5% risk when none of these risk factors was present (low-risk MGUS). However, the prognostic value of the free light-chain ratio has not yet been validated in other series of patients with MGUS.

Rosiñol *et al.*⁶¹ recognized two subsets of SMM: (1) the 'evolving' variant of SMM, characterized by a progressive increase in the M-protein size until symptomatic myeloma develops, a shorter time to progression and a previously recognized MGUS in most patients and (2) the nonevolving type, with a long-lasting stable M-protein, longer time to progression and no previous MGUS. It is our belief that eventually all patients with the evolving variant have a previous MGUS, also with an evolving pattern, with the evolving SMM representing the transition phase between MGUS and symptomatic MM. Importantly, we found a different cytogenetic pattern by comparative genomic hybridization for the two variants of SMM, with the pattern of the evolving type being very similar to that observed in patients with *de novo* symptomatic multiple myeloma.⁶² On the basis of these observations in SMM, the evolution pattern of our patients with MGUS was also investigated. We found that about 10% of these patients have an evolving type as defined by a slow but progressive increase in the M-protein size during the first 3 years of follow-up. It must be mentioned that the evolving pattern was the most important risk factor for malignant transformation, even with a higher impact than the plasma cell mass.⁴⁹ Thus, the actuarial transformation rates at 10 years of follow-up were 55 and 10% in patients with 'evolving' and 'nonevolving', respectively.

Table 3 Actuarial probability of malignant evolution of monoclonal gammopathy of undetermined significance

Reference	No. of patients	% Probability at		
		10 years	20 years	25 years
Kyle <i>et al.</i> (2004) ⁷	241	17	34	39
Pasqualetti <i>et al.</i> (1997) ⁵³	263	15	31	—
Cesana <i>et al.</i> (2002) ⁵⁴	1104	14	—	—
Kyle <i>et al.</i> (2002) ³¹	1384	12	25	30
Montoto <i>et al.</i> (2002) ⁵⁵	434	15	34	—

Table 4 Predictors of malignant transformation

Reference	No. of patients	M-protein size	BMPC (%)	M-protein type	Others
Kyle <i>et al.</i> (2004) ⁷	241	—	—	—	—
Bladé <i>et al.</i> (1992) ⁵⁶	128	—	—	IgA > IgG, IgM	—
Baldini <i>et al.</i> (1996) ⁵⁷	386	+	+	—	↓ Polyclonal Igs
Pasqualetti <i>et al.</i> (1997) ⁵³	263	—	—	—	—
Gregersen <i>et al.</i> (2001) ⁵⁸	1247	+	ND	IgA > IgG, IgM	Female
Cesana <i>et al.</i> (2002) ⁵⁴	1104	+	+	IgA, IgM > IgG	LC proteinuria, ↑ ESR, ↓ polyclonal Igs
Kyle <i>et al.</i> (2002) ³¹	1384	+	—	IgA, IgM > IgG	—
Rosiñol <i>et al.</i> (2007) ⁵⁹	359	+	+	IgA > IgG, IgM	'Evolving'

Abbreviations: BMPC, bone marrow plasma cell; ESR, erythrocyte sedimentation rate; ND, not determined.

Consequently, the evolving MGUS could be considered as an early myeloma, whereas the nonevolving type would be a true stable MGUS requiring a second hit for malignant transformation (Figure 1).

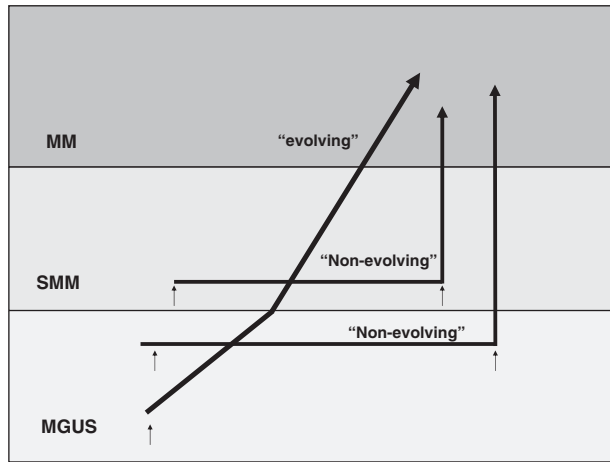


Figure 1 Possible evolution patterns of asymptomatic monoclonal gammopathies. Most asymptomatic monoclonal gammopathies, particularly MGUS, remain stable from its recognition until progression to symptomatic MM occurs. However, about 10% patients with MGUS show a progressive increase in the M-protein size leading to SMM and finally to symptomatic myeloma. The 'evolving' MGUS would be consistent with 'slowly evolving' or 'early' myeloma from the time of its appearance, in contrast with the stable or 'true' MGUS. MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.

Most recently, it has been shown that the presence of an aberrant phenotype by multiparameter flow cytometry of bone marrow plasma cells (95% or more aberrant phenotype: absence of CD19 and/or CD45, decreased expression of CD38 and overexpression of CD56) (Figure 2) is an important variable for predicting the risk of early progression from MGUS to MM.⁶³ Thus, the actuarial probability of malignant transformation at 10 years of follow-up for patients with 95% or greater versus less than 95% aberrant bone marrow plasma cells was 75 versus 15%, respectively. Similarly, among patients with SMM with more and less than 95% aberrant plasma cell phenotype, the actuarial probability of progression at 5 years was 64 and 8%, respectively.⁶³

Follow-up recommendations

Although there are no formal guidelines on follow-up in patients with MGUS, the usual practice is to re-evaluate them annually to detect multiple myeloma before complications, such as renal failure or pathological fractures, occur. Follow-up testing should include total serum protein with serum protein electrophoresis, 24 h urine protein excretion with urine electrophoresis, hemoglobin level as well as serum creatinine and calcium concentration. The monoclonal protein usually remains stable until myeloma develops. As mentioned above, some patients have 'evolving' MGUS. These patients more likely have slowly evolving myelomas rather than 'true' MGUS and require close follow-up. The recognition of different risk groups has important implications for follow-up. Likely, novel insights into the roles of molecular markers as well as environmental factors will influence our abilities to predict myeloma progression in the future. Such understandings will have a direct impact on our

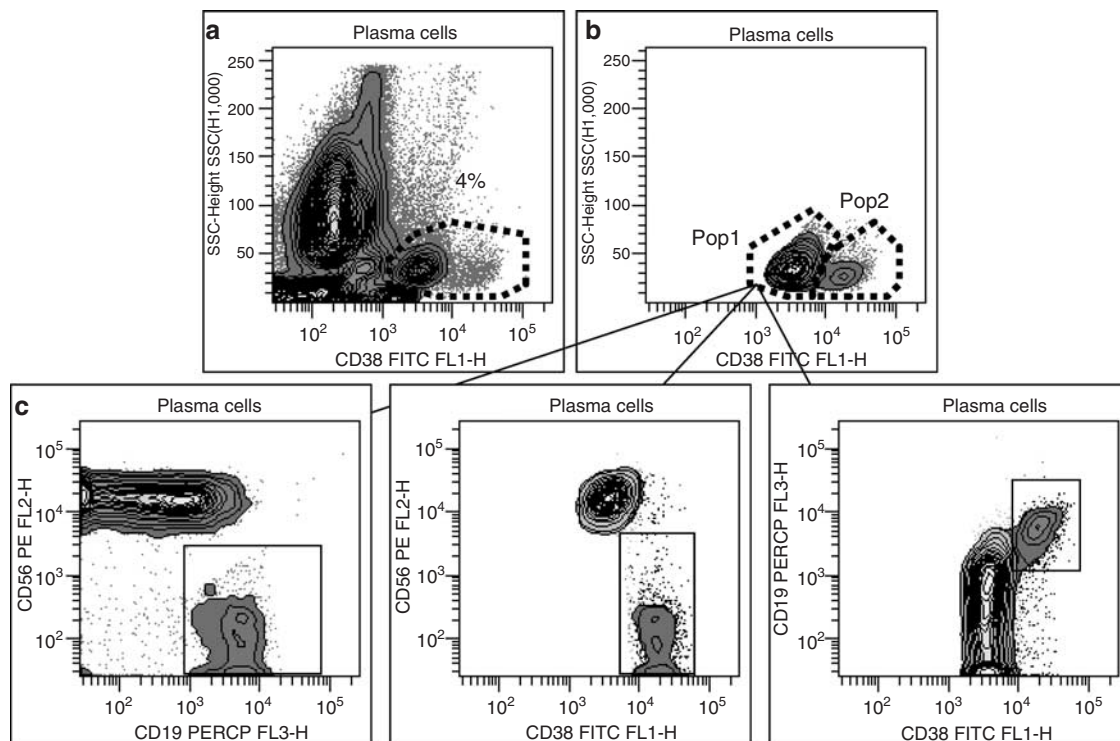


Figure 2 Phenotype of normal and abnormal plasma cells. (a) Plasma cells are characterized by high CD38 expression. (b) After selecting plasma cells, two populations with different amounts of CD38 are observed. (c) Population 1 (Pop1) corresponds to abnormal plasma cells (CD38dim CD19-/+ CD56bright) and population 2 (Pop2) corresponds to normal plasma cells (CD38strong CD19+ CD56-/+).

follow-up strategies. Currently, our group feels that patients with an IgG M-protein size lower than 1.5 g per 100 ml may not warrant follow-up for their MGUS because of the very low lifetime risk of malignant transformation.^{9,21} Additionally, the finding of a normal free light-chain ratio in these patients would further support no need for follow-up, as the actuarial and real probabilities of malignant transformation are 5 and 2%, respectively.⁶⁰ This is important because about 40% patients with MGUS have low-risk disease (IgG type, M-protein size <1.5 g per 100 ml, and normal free light-chain ratio).⁵⁹ In contrast, it is important to maintain a yearly follow-up policy for patients with high-risk (non-IgG, M-protein size >1.5 g per 100 ml and an abnormal free light-chain ratio), as their actuarial probability of malignant transformation at 20 years of follow-up approaches 60%.⁶⁰

Conclusion and future directions

In whites, MGUS has a high prevalence in individuals older than 50 years. In MGUS, the plasma cell clone has the molecular genetic features and the abnormal phenotypic profile observed in myelomatous genetic cells. When compared with whites, blacks have been found to have around two- and threefold higher prevalence rates of MGUS and MM, respectively. However, the risk of progression from MGUS to MM has been found to be very similar in whites and blacks. Indeed, once the MGUS clone is established, the average progression rate is 1% per year, but the molecular basis for its progression is unknown. The average actuarial progression rate at 10 years of follow-up ranges from 12 to 17% and from 25 to 34% at 20 years. The main factors associated with malignant transformation in MGUS are: (1) high plasma cell mass (M-protein size and/or percentage of bone marrow plasma cells), (2) IgA type versus others, (3) abnormal immunoglobulin free light-chain ratio, (4) the evolution pattern ('evolving' versus 'nonevolving') and (5) the ratio between phenotypically aberrant and normal plasma cells. Although the characterization of MGUS by molecular genetic studies will likely result in a more accurate risk stratification for individual patients, the recently recognized predictors of outcome will be helpful for better monitoring and hopefully for the investigation of treatment strategies with novel non-cytotoxic agents aimed at avoiding or delaying the progression in high-risk patients. Finally, there are several fundamental questions that remain to be answered. Are all myelomas preceded by MGUS? What are the actual patterns of MGUS spikes and other protein abnormalities prior to MM onset? How do the genetic abnormality patterns progress overtime from MGUS to MM in the same individual? Which are the mechanisms that control and maintain the plasma cell clone in a stable MGUS state? Future prospective studies are needed to address these issues.

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