From Myeloma Precursor Disease to Multiple Myeloma: New Diagnostic Concepts and Opportunities for Early Intervention

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Abstract
Since monoclonal gammopathy of undetermined significance (MGUS) was first described more than 30 years ago, the definition of the entity has evolved. Today, 3 distinct clinical MGUS subtypes have been defined: non-immunoglobulin M (IgM; IgG or IgA) MGUS, IgM MGUS, and light chain MGUS. Each clinical MGUS subtype is characterized by unique intermediate stages and progression events. Although we now have strong evidence that multiple myeloma is consistently preceded by a precursor state at the molecular level, there is urgent need to better understand mechanisms that regulate transformation from precursor to full-blown multiple myeloma. In the future, if such knowledge was available, it would allow clinicians to define high-risk and low-risk precursor patients for a more tailored clinical management. Also, it would provide insights on the individual patient’s disease biology, which, in turn, can be used for targeted and more individualized treatment strategies. On the basis of current clinical guidelines, patients diagnosed with MGUS and smoldering myeloma should not be treated outside of clinical trials. In the near future, it seems reasonable to believe that high-risk precursor patients will likely become candidates for early treatment strategies. In this review, we discuss novel insights from recent studies and propose future directions of relevance for clinical management and research studies.

Introduction
Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder present in more than 3% of the general Caucasian population age 50 and older (1, 2). On a clinical note, individuals diagnosed with MGUS have a 1% annual risk of progression to multiple myeloma (MM) or related malignancy (3). Typically, MGUS is found incidentally during the work-up of a variety of symptoms and disorders. It is characterized by abnormal immunoglobulins detectable in the patient’s peripheral blood and/or urine, as well as clonal plasma cells present in the bone marrow (Fig. 1). Definitions of distinct MGUS subtypes are given in Table 1.

Furthermore, MGUS has confirmed and reported associations with numerous diseases that are commonly encountered in clinical practice, such as osteoporosis and venous thrombosis (4). Given the fact that MGUS is easily detected in peripheral blood and it can be monitored noninvasively, MGUS represents a readily accessible model to study the conversion of premalignancy to malignancy (5).

Race and ethnicity play a role in the pathogenesis of MGUS. African Americans and blacks from Africa have a 2- to 3-fold higher prevalence of MGUS compared with whites (6, 7). In contrast, the risk is lower in Asians from Japan (8) and in Mexicans (9). Increasing age (1), male gender, family history of MGUS and/or MM (10), immunosuppression, and exposure to certain pesticides (11) all increase the risk of MGUS. Clearly, future studies are needed to improve our understanding on underlying mechanisms of these associations.

A more advanced premalignant stage of plasma cell proliferation in non-immunoglobulin M (IgM) MGUS is termed smoldering myeloma and is characterized by a much higher risk of progression to MM (on average, about 10% per year during the first 5 years of follow-up; ref. 12).

During recent years, new concepts and advances have emerged about the diagnosis, classification, risk stratification, and management of myeloma precursor disease (MGUS and smoldering myeloma). In this review, we discuss novel insights from recent studies and propose future directions for clinical management and research studies (13).

Distinct Clinical Monoclonal Gammopathy of Undetermined Significance Subtypes

Since MGUS was first described in 1978 (14), the definition of the entity has evolved (15). Today, 3 distinct clinical
MGUS subtypes have been defined: non-IgM (IgG or IgA) MGUS, IgM MGUS, and light chain MGUS (Table 1). Each clinical MGUS subtype is characterized by unique intermediate stages and progression events. For example, as mentioned above, the more advanced premalignant stage of plasma cell proliferation in non-IgM MGUS is smoldering myeloma; it has an average 10% annual risk of progression to MM (versus 1% per year collectively for all forms of MGUS; ref. 12). IgM MGUS is associated with a predisposition mainly to Waldenström’s macroglobulinemia and rarely to IgM MM (16, 17). Recently, a new disease entity termed “light chain MGUS” was defined. It represents the premalignant precursor of a subtype of MM called “light chain MM,” which accounts for almost 20% of all new MM cases (18). The equivalent of smoldering myeloma and smoldering Waldenström’s macroglobulinemia in the spectrum of light chain monoclonal gammapathies is called idiopathic Bence Jones proteinuria (Table 1; refs. 19, 20). At this time, at least 1 large cohort, including patients meeting each of the above listed clinical subtypes, has been assembled. These cohorts have allowed clinicians and researchers to study and define the natural history for each MGUS subtype (3, 12, 16, 18, 19, 21–23). Consequently, we now know how to diagnose each of these entities accurately, and we also know the outcome of patients meeting the specific subtype definition to assist with management and counseling. In Table 1, we have summarized the main features and results from the largest epidemiologic and clinical studies focusing on MGUS subtypes to date (3, 12, 16, 18, 19, 21–23). More specifically, we have listed and commented on prevalence, risk of progression, and natural history of non-IgM MGUS, IgM MGUS, and light chain MGUS.

It should be emphasized that, in patients diagnosed with clonal proliferation of plasma cells consistent with a precursor state, the biology and natural history is very different compared with patents diagnosed with MM. Importantly, patients with a precursor state should be reassured rather than labeled as having a cancer. For example, patients with less than 10% infiltration of the bone marrow by lymphoplasmacytic cells have an overall survival similar to that of the general population and should, therefore, not be labeled as having a lymphoma or Waldenström’s macroglobulinemia merely because the bone marrow pathology shows clonal proliferation of lymphoid cells (22). Furthermore, on a clinical note, increasingly better sensitivity for diagnostic methods will continue to challenge clinical management, and the line between malignancy and premalignancy will most likely continue to blur. As our understanding of disease progression improves, it will become more and more important to recognize that well-designed epidemiologic studies and clinicopathologic disease
definitions will be required to separate patients who need treatment, such as chemotherapy or stem cell transplantation for cancer like myeloma (24), from those who call for no therapy and need reassurance (5).

From Precursor to Multiple Myeloma: Current Clinical Risk Models

It is important to keep in mind that the vast majority of MGUS patients will never progress to MM. Currently, we do not have access to any reliable markers to predict risk of MM progression for individual MGUS patients. At the present time, the risk of progression of MGUS is assessed by a few selected risk factors. Two major models for risk stratification have been proposed: one model by the Mayo Clinic and the other by the Spanish study group [Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA); Fig. 2].

The Mayo Clinic model focuses largely on serum protein abnormalities. For MGUS patients, the following features are considered as adverse risk factors: non-IgG isotype, M-protein concentration ≥ 1.5 g/dL, and an abnormal serum free light chain (FLC)–ratio (normal reference 0.26 to 1.65; Fig. 2; ref. 25). In the Mayo Clinic model, at 20 years of follow-up, MGUS patients with all 3 risk factors, on average, have an absolute risk of MM progression of 58%; for MGUS patients with 2, 1, and 0 of these risk factors, the corresponding absolute risk is 37%, 21%, and 5%, respectively (25). For smoldering myeloma patients, the following features are considered to be adverse risk factors: ≥ 3 g/dL M protein, an FLC ratio outside the reference range of 0.125 to 8, and ≥10% bone marrow plasma cells (BMPC; Fig. 2; refs. 14, 26). In the Mayo Clinic model, at 5 years of follow-up, smoldering myeloma patients with all 3 risk factors, on average, have a cumulative risk of MM progression of 76% [median time to progression (TTP) was 1.9 years]; for patients with 2 or 1 risk factors the corresponding risk was 51% (median TTP 5.1 years) and 25% (median TTP 10 years), respectively (12, 26).

The Spanish model uses multiparametric flow cytometry of bone marrow aspirates to differentiate aberrant from normal plasma cells (27). Plasma cells characteristically express CD138 and intense (bright) CD38. The features of aberrant plasma cells (aPC) included decreased CD38 expression, expression of CD56, and the absence of CD19 and/or CD45. In 93 smoldering myeloma and 407 MGUS patients, the percentage of phenotypically aPCs of total BMPCs at diagnosis allowed risk stratification of MGUS and smoldering myeloma patient’s progression to overt MM. In their study, MGUS and smoldering myeloma patients with ≥95% aPCs/BMPC at diagnosis had a significantly higher risk of MM progression (27). Furthermore, on multivariate analysis, ≥95% aPCs/BMPC, DNA aneuploidy, and immunoparesis were found to be independent predictors of MM progression. More specifically, for MGUS patients with 0, 1, or 2 risk factors (≥95% aPCs/ BMPC and DNA aneuploidy) the risk of progression at 5 years was 2%, 10%, and 46%, respectively (Fig. 2). For smoldering myeloma patients (risk factors: ≥95% aPCs/ BMPC and immunoparesis), the corresponding risks at 5 years were 4%, 46%, and 72%, respectively (Fig. 2; ref. 27).

Taken together, these studies emphasize the fact that the risk of MM progression varies greatly among individuals diagnosed with myeloma precursor disease. As discussed in detail below, we need better markers to define high-risk (versus low-risk) MGUS–smoldering myeloma and to better predict individual risk of MM progression.

From Precursor to Multiple Myeloma: Current Knowledge from the Research Laboratory

Two independent studies have shown that MM is consistently preceded by MGUS (28, 29). In the first study, on the basis of a large cancer-screening trial including 77,469 volunteers prospectively followed for up to 10 years in a cancer-screening trial, 71 individuals were found to develop MM. Using stored prediagnostic serum samples obtained annually from these subjects, evidence of MGUS was shown prior to MM in all participants (28). In 82% of MM cases, evidence of MGUS was present in prediagnostic blood collected ≥8 years prior to MM diagnosis (28). The other study was based on a large U.S. Army serum repository. In brief, that study reported that 27 of 30 MM cases with available prediagnostic serum samples had evidence of a preceding MGUS diagnosis, the other 3 patients either had IgD MM or lacked samples ≤8 years prior to MM diagnosis (29).

Of great relevance from a clinical perspective, in approximately half of the 71 MM patients from the large cancer-screening trial (28), on the basis of the systematically collected prediagnostic blood samples, the M-protein concentration increased annually following initial detection; among the remaining patients, serum M protein was stable until MM diagnosis (30). Similar patterns of gradual evolution and sudden increase prior to diagnosis were also observed in the serum FLC ratio (around 85% had a skewed FLC ratio 2 years prior to MM diagnosis; ref. 28). Importantly, these findings emphasize the fact that clinicians must be alert in monitoring patients for myeloma-related end-organ damage regardless of the stability of serum protein markers.

At the molecular level, on the basis of our current knowledge, transformation from precursor to full-blown MM does not seem to be a sudden, discontinuous process with specific immunophenotypic markers differentiating plasma cells in patients with MGUS, smoldering myeloma, and MM (31, 32). Instead, several overlapping oncogenic events within plasma cells and the marrow microenvironment accumulate from normal plasma cells through precursor disease to full-blown MM. Indeed, early cytogenetic changes are seen among almost all patients at the level of MGUS (31, 32). These potentially overlapping, enduring changes are seen from MGUS onward and include hyperdiploidy and primary immunoglobulin translocations at the 14q32 locus (33–35). In both states, cyclin D dysregulation is a very common early event (36). Importantly, at
this time, MGUS from smoldering myeloma cannot be differentiated using conventional cytogenetics or FISH (37).

Abnormal plasma cells in MGUS, smoldering myeloma, and MM produce a broad range of immunoreceptors that are stimulated by both exogenous molecules and microenvironmental paracrine signals, such as interleukin-6, contributing to the clonal proliferation observed in patients’ bone marrow biopsies (38). In contrast, many secondary oncogenic events have been implicated in the transition from MGUS and/or smoldering myeloma to full-blown MM and from newly diagnosed MM to advanced and/or refractory disease. These secondary genetic events may, in part, be dependent on the primary lesion (39, 40). Furthermore, complex alterations to microenvironmental interactions occur in the transition from MGUS to MM (41). An apparent manifestation in myeloma genesis is the interaction between abnormal plasma cells, cells in the bone marrow microenvironment, and the bone (41), which ultimately leads to characteristic lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder.

### Table 1. Disease Definitions for the Monoclonal Gammopathies: Monoclonal Gammopathy of Undetermined Significance and Related Disorders

<table>
<thead>
<tr>
<th>Type of monoclonal gammopathy</th>
<th>Premalignancy with a low risk of progression (1 to 2% per year)</th>
<th>Premalignancy with a high risk of progression (10% per year)</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG and IgA (non-IgM) monoclonal gammopathies</td>
<td>Non-IgM MGUS</td>
<td>Smoldering MM</td>
<td>MM</td>
</tr>
<tr>
<td>All 3 criteria must be met:</td>
<td>Both criteria must be met:</td>
<td>All 3 criteria must be met except as noted:</td>
<td></td>
</tr>
<tr>
<td>- Serum monoclonal protein &lt; 3 g/dL</td>
<td>- Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL and/or clonal BMPCs ≥ 10%, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clonal BMPCs &lt; 10%, and</td>
<td>- Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to the plasma cell proliferative disorder</td>
<td></td>
<td></td>
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<tr>
<td>- Absence of end-organ damage such as CRAB that can be attributed to the plasma cell proliferative disorder</td>
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Treatment Studies for Smoldering Myeloma: Future Challenges and Opportunities

On the basis of the International Myeloma Working Group 2010 guidelines, patients diagnosed with MGUS and smoldering myeloma should not be treated outside of clinical trials (2). Overall, treatment trials for MGUS patients are complicated, as these individuals are relatively healthy and the majority has a low life-time risk of progression, especially when other causes of death are taken into account (3). Therefore, it seems reasonable to propose that an ideal treatment would be effective, nontoxic, and directed toward patients with a high risk of progression. At this time, we do not have access to any such drug.

In contrast to MGUS, early treatment strategies for smoldering myeloma are particularly attractive, as the rate of progression is higher than in MGUS patients (4). Table 1 presents definitions for the monoclonal gammopathies, including IgM monoclonal gammopathies (IgM MGUS), Smoldering Waldenström’s macroglobulinemia, and IgM myeloma.

Table 1. Disease Definitions for the Monoclonal Gammopathies: Monoclonal Gammopathy of Undetermined Significance and Related Disorders (Cont’d)

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<th>Premalignancy with a high risk of progression (10% per year)</th>
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</tr>
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<tr>
<td>IgM monoclonal gammopathies</td>
<td>IgM MGUS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Smoldering Waldenström’s macroglobulinemia</td>
<td>Waldenström’s macroglobulinemia</td>
</tr>
<tr>
<td>All 3 criteria must be met:</td>
<td>Serum IgM monoclonal protein &lt; 3 g/dL, and/or bone marrow lymphoplasmacytic cells &lt; 10%, and Absence of end-organ damage such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.</td>
<td>Both criteria must be met: Serum IgM monoclonal protein ≥ 3 g/dL and/or bone marrow lymphoplasmacytic infiltration ≥ 10%, and No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.</td>
<td>All criteria must be met: IgM monoclonal gammopathy (regardless of the size of the M protein), and ≥ 10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (e.g., surface IgM&lt;sup&gt;+&lt;/sup&gt;, CD5&lt;sup&gt;+&lt;/sup&gt;, CD10&lt;sup&gt;+&lt;/sup&gt;, CD19&lt;sup&gt;+&lt;/sup&gt;, CD20&lt;sup&gt;+&lt;/sup&gt;, CD23&lt;sup&gt;+&lt;/sup&gt;) that satisfactorily excludes other lymphoproliferative disorders including chronic lymphocytic leukemia and mantle cell lymphoma. Evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.</td>
</tr>
<tr>
<td>IgM myeloma</td>
<td>All criteria must be met: Symptomatic monoclonal plasma cell proliferative disorder characterized by a serum IgM monoclonal protein regardless of size Presence of 10% plasma cells on bone marrow biopsy Presence of lytic bone lesions related to the underlying plasma cell disorder and/or translocation t(11;14) on FISH.</td>
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progression to MM is substantially higher. Prior to the advent of novel therapies, a randomized-controlled trial of melphalan-prednisone given initially versus at progression to MM found no difference in response rate or overall survival (46). Furthermore, a single-arm trial using thalidomide and pamidronate in 76 patients with smoldering myeloma failed to show a clear benefit for treatment, with a quite unexpected shorter TTP among treatment responders versus nonresponders (47). In their report, the authors speculated that their observation, perhaps, was reflecting greater drug sensitivity of more aggressive disease (47). Another randomized trial (zoledronic acid versus surveillance during 1 year) found reduced skeletal complications at progression from smoldering myeloma to MM, but without impact on the risk of progression (48). It is unknown whether a more extended bisphosphonate treatment influences the risk of progression. The study based on zoledronic acid versus surveillance was prematurely stopped by the safety committee because of development of osteonecrosis of the jaw in a smoldering myeloma patient in the treatment arm (48). Currently, a randomized, multicenter phase III trial for patients with high-risk smoldering myeloma is ongoing in Spain (lenalidomide-dexamethasone versus active surveillance). An interim analysis at 19 months of follow-up shows that about 50% of patients in the surveillance arm experienced progression to MM, whereas only 2 patients in the treatment arm had progression (49). A collaborative Eastern Cooperative Oncology Group (ECOG)–Southwest Oncology Group (SWOG) study, based on lenalidomide versus active surveillance, just opened in the United States. Importantly, at the American Society of Hematology (ASH) meeting in December of 2010, a few studies reported an increased occurrence of second malignancies in MM after extended dosing with lenalidomide, which was given as a maintenance therapy following high-dose melphalan.

Table 1. Disease Definitions for the Monoclonal Gammopathies: Monoclonal Gammopathy of Undetermined Significance and Related Disorders (Cont’d)

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</tr>
</thead>
<tbody>
<tr>
<td>Light chain monoclonal gammopathies</td>
<td>Light chain MGUS</td>
<td>Idiopathic Bence Jones proteinuria</td>
<td>Light chain MM&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>All criteria must be met:</td>
<td>Abnormal FLC ratio (&lt; 0.26 or &gt; 1.65)</td>
<td>Urinary monoclonal protein on urine protein electrophoresis ≥ 500 mg/24 h and/or clonal BMPCs ≥ 10%</td>
<td>Same as MM except no evidence of immunoglobulin heavy chain expression</td>
</tr>
<tr>
<td>Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio &gt; 1.65 and increased lambda FLC in patients with ratio &lt; 0.26)</td>
<td>No immunoglobulin heavy chain expression on immunofixation</td>
<td>No immunoglobulin heavy chain expression on immunofixation</td>
<td></td>
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<tr>
<td>No immunoglobulin heavy chain expression on immunofixation</td>
<td></td>
<td>Absence of end-organ damage such as CRAB that can be attributed to the plasma cell proliferative disorder</td>
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<tr>
<td>Clonal BMPCs &lt; 10%, and</td>
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<td>Absence of end-organ damage such as CRAB that can be attributed to the plasma cell proliferative disorder</td>
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</table>

Abbreviation: CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions.

<sup>a</sup>Occasionally patients with IgD and IgE monoclonal gammopathies have been described and will be considered to be part of this category as well.

<sup>b</sup>Note that, conventionally, IgM MGUS is considered a subtype of MGUS, and similarly, light chain MM is considered a subtype of MM. Unless specifically distinguished, when the terms MGUS and MM are used, in general, they include IgM MGUS and light chain MM, respectively.

Reproduced with permission from Rajkumar et al. (53).
predictors of MM progression from MGUS and/or smoldering myeloma. More specifically, for MGUS patients were found to be risk factors for progression. For smoldering myeloma patients, the risk factors were of MM progression (27). Furthermore, on multivariate analysis, MGUS and smoldering myeloma patients with (bright) CD38. The features of aPCs included decreased CD38 expression, expression of CD56, and the absence of CD19 and/or CD45. In their study, cytometry of bone marrow aspirates to differentiate aberrant from normal plasma cells (27). Plasma cells characteristically express CD138 and intense g/dL M protein, an FLC ratio outside the reference range of 0.125 to 8, and serum FLC ratio (normal reference 0.26 to 1.65; ref. 25). For smoldering myeloma patients, the following features are considered to be adverse risk factors: non-IgG isotype, M-protein concentration is currently unknown whether treating smoldering myeloma patients improves overall survival and/or quality of life, as such data are not yet available. As stated above, in accord with the International Myeloma Working Group 2010 guidelines, smoldering myeloma patients should not be treated outside of clinical trials (2).

Although the above discussed trials underscore the value of ongoing treatment trials for smoldering myeloma patients, one can envision several scenarios resulting from treatment of smoldering myeloma. Aimed at preventing progression, smoldering myeloma could be treated as a chronic disease, with an extended dosing schema used to control the malignant clone (Fig. 3). Alternately, in the future, highly active therapy could be used with the goal of cure. However, to responsibly carry out any such trial, well-designed correlative studies must be done to assess for the theoretical possibility of unexpected long-term adverse events or selecting for more aggressive disease (Fig. 3).

**Future Directions**

In the context of numerous molecular events and heterogeneous risk of progression, developing individualized risk profiles for patients with MGUS and smoldering myeloma represents an ongoing challenge. Clearly, we need future prospective studies based on clinical monitoring and extensive correlative science. The ultimate goal is to develop better molecular markers that will allow (i) clinicians to define high-risk and low-risk precursor patients for a more tailored clinical management, and (ii) to provide insights on the individual patient’s disease biology, which in turn can be used for targeted and more individualized treatment strategies. In the near future, it seems reasonable to believe that high-risk precursor patients will likely become candidates for early treatment strategies. As discussed in detail in this review, future studies need to assess the role of early treatment in relation to overall survival and quality of life (50–52). High response rates among smoldering myeloma patients receiving treatment may not correlate with survival (50, 52). In fact, one may speculate that prolonged “stable disease” may provide key benefit to patients.
Currently, the answers to these important questions remain unknown.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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