Published in final edited form as:

JAMA. 2010 December 01; 304(21): 2397–2404. doi:10.1001/jama.2010.1713.

Multiple Myeloma Precursor Disease

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Abstract

Recent data indicate that multiple myeloma is consistently preceded by the precursor states of monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma. Currently, multiple myeloma is a clinical diagnosis based on manifestations including hypercalcemia, renal failure, anemia, and bone lesions, whereas MGUS and smoldering myeloma are diagnosed based on laboratory abnormalities. Current clinical markers allow for more individualized risk stratification and counseling of these patients. However, there is a dearth of biomarkers and molecular imaging techniques capable of (1) accurately identifying patients with disease biology corresponding with high risk of progression; (2) elucidating the mechanism of transformation to multiple myeloma; and (3) forming a framework for development of targeted therapies. This case presentation and review discusses the current understanding of myeloma precursor disease and future opportunities for improving personalized management of patients with MGUS or smoldering myeloma, as well as the potential for developing early treatment strategies designed to delay and prevent development of multiple myeloma.

CASE PRESENTATION

The patient is a healthy 72-year-old white man with smoldering myeloma diagnosed 6 months ago and an 11-year history of monoclonal gammopathy of undetermined significance (MGUS) undergoing interval follow-up (Figure 1). His diagnosis of MGUS was first detected in 1999 during an annual physical when serum protein electrophoresis (SPEP) was ordered as part of a broad panel of blood tests; all other results were within their normal ranges.

In 2009, during a follow-up visit, laboratory values included creatinine 1.22 mg/dL, calcium 8.80 mg/dL, hemoglobin 12.6 g/dL, and albumin 4.3 g/dL (to convert values to SI units multiply creatinine by 88.4 for $\mu\text{mol/L}$; calcium by 0.25 for mmol/L; hemoglobin by 10 for g/L; and albumin by 10 for g/L, respectively). The patient's values, as revealed by SPEP

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Additional Contributions: We thank the patient for providing permission to publish case details. We also acknowledge the expert review of Figure 2 by Irina Maric, MD, at the National Institutes of Health; Figure 3 by Constance Yuan, MD, PhD; Figure 4 by Peter Choyke, MD; and Figure 5 by Michael Kuehl, MD, all at the National Cancer Institute.

Role of the Sponsor: The Intramural Research Program of the National Cancer Institute of the National Institutes of Health had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation of the manuscript. Before submission, the manuscript underwent a standard administrative review at the National Cancer Institute.

Financial Disclosure: None reported.

were 4.4 g/dL for monoclonal protein (M protein), 5780 mg/dL for a highly elevated IgG, 47 mg/dL for a decreased level of IgA, and less than 21 mg/dL for a decreased level of IgM (to convert values to SI units multiply IgG by 0.01 for g/L; and IgA and IgM by 10 for mg/L, respectively). The ratio of serum κ free light chains (FLC) to λ FLC was 2.44 (normal range, 0.26-1.65). Bone marrow biopsy demonstrated 40% CD138⁺ κ -restricted plasma cells (Figure 2). Flow cytometry of the aspirate revealed almost all plasma cells were immunophenotypically abnormal (Figure 3). Skeletal survey showed negative results for lytic lesions, although an outside fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) displayed mild FDG uptake in the sacrum.

At a follow-up visit 2 months later, the patient expressed concern of lower back pain located in the sacrum and left iliac bone areas. M-protein level was 4.9 g/dL. The back pain increased and magnetic resonance imaging (MRI) was conducted to rule out cord compression. Furthermore, a repeat FDG PET/CT revealed focal lesions in the sacrum and left iliac bone with a standard uptake value of 3.4 and 2.8, respectively (Figure 4). A diagnosis of multiple myeloma was made and treatment options were explained. The patient began treatment with lenalidomide/dexamethasone with partial response after 3 cycles.

COMMENT

Multiple myeloma is a malignancy of plasma cells in the bone marrow resulting in the production of excess M-protein, FLC, or both combined.² Common initial presentations include bone pain, pathologic fractures, malaise, and incidental diagnosis from comprehensive laboratory and imaging studies.³ An estimated 20 580 new cases of multiple myeloma were diagnosed in the United States in 2009.⁴ Median survival is 3 to 4 years following diagnosis, although survival appears to have improved since the advent of novel therapies such as autologous stem cell transplantation, immunomodulatory drugs (thalidomide and lenalidomide), and proteasome inhibitors (bortezomib).^{5,6}

The 2 known precursors to multiple myeloma, MGUS and smoldering myeloma, were first described by Kyle and Greipp in 1978 and 1980, respectively, as the presence of an M protein in the serum and/or excess bone marrow plasma cells in the absence of clinical evidence of either multiple myeloma or another lymphoproliferative disorder.^{7,8} Although MGUS was found to have a stable 1% annual risk of progression to multiple myeloma, smoldering myeloma was found to have a 10% annual risk probability of progression for the first 5 years, decreasing to 3% annually for the following 5 years, and then reaching the same 1% risk as MGUS thereafter.^{9,10} Screening studies have found MGUS present in approximately 3.2% of white individuals older than 50 years.¹¹ Prevalence appears to be roughly twice as high among African, African American, and obese individuals.^{12,13}

In response to inconsistent definitions used in the past, in 2003 the International Myeloma Working Group (IMWG) developed consensus definitions of the known monoclonal gammopathies.¹⁴ MGUS was defined as the presence of serum M protein at a level of less than 3 g/dL with fewer than 10% monoclonal plasma cells in the bone marrow; smoldering myeloma was defined as either serum M protein at a level of at least 3 g/dL or at least 10% monoclonal plasma cells in the bone marrow. In contrast to these laboratory-based

definitions, a diagnosis of multiple myeloma is based on the clinical assessment of myeloma-related end-organ impairment in the presence of an M protein, monoclonal plasma cells, or both. End-organ damage was defined using both the classic criteria of hypercalcemia (serum calcium >11.5mg/dL), renal failure (defined by creatinine >1.95mg/dL with no other etiology), anemia (hemoglobin <10 g/dL), or skeletal lesions (lytic lesions by skeletal survey, osteoporosis with pathologic fractures, or cord compression), and additional criteria including recurrent bacterial infections (>2 in 12 months), amyloidosis, or symptomatic hyperviscosity. Because recent data have shown that several typical oncogenic events observed in newly diagnosed multiple myeloma (Figure 5) may be present at the level of MGUS, these cannot be used to differentiate the 2 entities.¹⁵

This judgment of end-organ damage forms the clinical dilemma of this patient's case. Initially meeting criteria for MGUS in 1999, his course was uneventful with only a gradual increase in M protein until November of 2009, at which time the finding of 40% plasma cells on bone marrow biopsy led to diagnosis of smoldering myeloma. Hypercalcemia, renal failure, anemia, and lytic lesions by skeletal survey were absent. However, intensifying back pain, increasingly abnormal laboratory values, and focal lesions by FDG PET/CT in the area of back pain were interpreted as multiple myeloma requiring treatment.

TRANSFORMATION TO MULTIPLE MYELOMA

Two recent, independent studies have shown that multiple myeloma is consistently preceded by MGUS.^{20,21} Of 77 469 participants prospectively observed for as many as 10 years in a cancer screening trial, 71 ultimately developed multiple myeloma. Assays for protein abnormalities in prediagnostic serum samples demonstrated prior evidence of MGUS in all participants; in 82% of multiple myeloma cases, evidence of MGUS was present at least 8 years prior to diagnosis.²⁰ Another recent study found that 27 of 30 multiple myeloma cases with prediagnostic serum samples available in a serum repository demonstrated preceding MGUS; the other 3 patients either had IgD multiple myeloma or lacked samples at least 8 years prior to multiple myeloma diagnosis.²¹

In approximately half of patients, the M protein concentration increased annually following initial detection; among the remaining patients, serum M protein was stable until multiple myeloma diagnosis. Similar patterns of gradual evolution and sudden increase prior to diagnosis were also observed in the serum FLC ratio.²⁰ Importantly, these findings demonstrate that clinicians must be vigilant in monitoring patients for myeloma-related end-organ damage regardless of the stability of serum protein markers.

At the molecular level, transformation to multiple myeloma does not appear to be a sudden, discontinuous process with specific immunophenotypic markers differentiating plasma cells in patients with MGUS, smoldering myeloma, and multiple myeloma. Rather, several overlapping oncogenic events within plasma cells and the marrow microenvironment accumulate from normal plasma cells through precursor disease to advanced multiple myeloma.

Early cytogenetic changes are seen among almost all patients at the level of MGUS. These potentially overlapping, enduring changes are seen from MGUS onward, and include hyperdiploidy and primary immunoglobulin translocations at the 14q32 locus.^{16,18,22} In both states, cyclin D dysregulation is a very common early event.²³ However, at the time of this study, MGUS from smoldering myeloma cannot be differentiated using conventional cytogenetics or fluorescent in situ hybridization.²⁴

The genomic complexity that characterizes plasma cell disorders permits cellular proliferation. Plasma cells in multiple myeloma and its precursors produce a broader than normal set 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.²⁵

In contrast, many secondary oncogenic events have been implicated in the transition from asymptomatic precursor disease to full-blown multiple myeloma and from newly diagnosed multiple myeloma to advanced/refractory disease (Figure 5). These secondary genetic events may, in part, be dependent on the primary lesion.^{15,17} Additionally, complex alterations to microenvironmental interactions occur in the transition from precursor disease to multiple myeloma.¹⁹ Perhaps the most clinically apparent of these are interactions between myelomatous plasma cells and skeletal components, which ultimately lead to characteristic lytic lesions in approximately 80% of multiple myeloma patients.²⁶ Although lytic lesions caused by osteoclastic activation, osteoblastic inactivation, or both combined is a criterion for progression from MGUS or smoldering myeloma to multiple myeloma, studies using quantitative bone biopsy and levels of RANK-ligand, a biomarker for bone turnover, have revealed excess bone resorption in patients with MGUS.^{27,28} Although undetectable by conventional imaging, osteoclast activation may occur earlier than previously believed.

RISK STRATIFICATION

Based on recent advances in immunophenotyping plasma cells and measuring serum FLC, 2 independent risk stratification schemes for MGUS and smoldering myeloma have been designed by the Mayo Clinic^{10,29,30} and the Spanish PETHEMA study group.³¹

The Mayo Clinic criteria are primarily based on the levels of SPEP with immunofixation and FLC assay. In a retrospective study of 1148 patients diagnosed with MGUS with long-term follow-up, M protein greater than 1.5 g/dL, non-IgG MGUS, and FLC ratio less than 0.26 or greater than 1.65 were independent risk factors for progression. At 20 years, patients with no risk factors had a 5% risk of progression, compared with 21%, 37%, and 58% for patients with 1, 2, or 3 risk factors.²⁹ Recently, a study screening for FLC abnormalities without a detectable M protein found a much lower risk of progression to multiple myeloma when compared with conventional MGUS.³² In a study observing 276 patients with smoldering myeloma, an M-protein level of at least 3 g/dL, bone marrow plasma cells of at least 10%, and FLC ratio deviating outside the nonstandard range of 0.125 to 8 were found to be independent risk factors for progression. At 5-year assessment, risk of progression to multiple myeloma was 25%, 51%, and 76% for patients with 1, 2, or 3 risk factors, respectively.^{10,30}

In contrast, the risk stratification scheme of the PETHEMA study group has focused on the use of multiparameter flow cytometry of the bone marrow to quantify the ratio of abnormal neoplastic plasma cells to normal plasma cells. At 5-year follow-up, patients with MGUS but without at least 95% abnormal neoplastic plasma cells or DNA aneuploidy were found to have a very small 2% risk of progression, compared with a 10% risk for patients with 1 risk factor and a comparatively high 46% risk of progression at 5 years for patients with both.³¹ For patients with smoldering myeloma, at least 95% of abnormal neoplastic plasma cells and reduction of uninvolved immunoglobulins were independent risk factors for progression, with rates of progression at 5 years being 4%, 46%, and 72% for patients with neither, 1, or both risk factors, respectively.³¹

Although the PETHEMA criteria may allow for greater differentiation of individual risk of progression, especially for identifying MGUS patients with very high risk of progression and smoldering myeloma patients with very low risk of progression, these criteria are limited by the requirement of a fresh bone marrow aspirate for all patients and flow cytometry panels that may not be available in all laboratories. In contrast, evaluation by the Mayo Clinic scheme is more readily available and allows the clinician to spare patients with low-risk MGUS from undergoing a bone marrow biopsy. Future prospective trials incorporating these and other potential markers of progression will likely improve risk stratification.

IMAGING

In current practice, imaging in MGUS and smoldering myeloma fulfills 2 roles: ruling out progression and monitoring for early complications. Currently, the metastatic bone survey (ie, skeletal survey) is the criterion standard for assessing osteolytic lesions, indicating progression to multiple myeloma. However, the skeletal survey is relatively insensitive and nonspecific for detecting myeloma-related bone disease; destruction of approximately 30% of trabecular bone in the area of the lytic lesion is required for detection.^{1,33} Despite these limitations, a skeletal survey is inexpensive and requires a relatively small dose of radiation to perform on the whole body.

More sensitive imaging techniques have been used to probe for early skeletal disease. Whole-body low-dose multidetector row CT has been shown to be highly sensitive in detecting osteolytic lesions smaller than 5 mm. With this technique, the number of patients with lesions was similar compared with skeletal survey, but radiation doses were high.^{34,35}

MRI may also detect focal lesions more sensitively than skeletal survey. A recent study using whole-body MRI in 149 patients with smoldering myeloma and negative findings from a skeletal survey found focal lesions in 28% of patients. Moreover, patients with focal lesions were more likely to progress to multiple myeloma than patients without.³⁶ Focal lesions confined to the bone marrow have been observed in MGUS patients.³⁷ These findings prompted a cross-sectional study of patients with MGUS, smoldering myeloma, and multiple myeloma using dynamic contrast-enhanced MRI, measuring wash-in and wash-out kinetics of a contrast agent in the bone marrow. Microcirculation patterns differed in MGUS compared with smoldering myeloma or multiple myeloma.³⁸ Further research incorporating

these markers of progression is needed to assess the potential to independently predict progression or increased morbidity from myeloma-related bone disease.

Functional imaging may prove useful to evaluate early bone disease, as activation of osteoclasts occurs prior to the appearance of osteolytic lesions on imaging.²⁷ Currently CT is also used in combination with FDG PET to assess response to therapy, with a standard uptake value of greater than 2.5 and corresponding lesion on CT defining myeloma-related lesions.³⁹ Data in MGUS and smoldering myeloma using FDG PET/CT are limited, although it is possible that bone-specific tracers such as 18-sodium fluoride injection may provide enhanced sensitivity to detect early lesions in patients with precursor disease.

MRI is currently the most capable modality for ruling out cord compression. MRI provides precise information regarding nerve level, size and extension of tumor mass, and extent of compression.³³ Additionally, MRI can differentiate osteoporotic- from myeloma-related compression fractures in patients with MGUS or smoldering myeloma. An epidural mass with low T1-and high T2-weighted signal implies a myeloma-related etiology.^{33,40}

CLINICAL MANAGEMENT

Traditionally, patients with MGUS or smoldering myeloma have been managed with an initial workup to (1) rule out multiple myeloma; and (2) confirm the diagnosis with subsequent interval follow-up. In June of 2010, the IMWG released consensus guidelines for monitoring and managing the cases of patients with MGUS and smoldering myeloma.¹

For the first time, these guidelines suggest risk stratifying all patients with MGUS and smoldering myeloma and differentially monitoring patients on the basis of their risk scores. Importantly, the recommendations state that for patients with low-risk MGUS by the Mayo Clinic criteria (IgG M protein <1.5 g/dL with normal FLC ratio) in the absence of concerning symptoms such as anemia or poor renal function, no further initial evaluation is needed. Subsequently, patients should be monitored for levels with SPEP, complete blood cell count, calcium, and creatinine at 6 months and every 2 to 3 years thereafter if stable. However, the new guidelines state that patients with any risk factor should have a baseline skeletal survey and bone marrow biopsy, with clinical follow-up at 6 months and annually thereafter. In the case of IgM MGUS, abdominal CT is recommended to assess retroperitoneal lymphadenopathy to rule out alternate lymphoproliferative processes.¹

In addition to monitoring patients for progression, additional risks must be considered among patients with MGUS. Although it has been known for some time that a diagnosis of multiple myeloma confers an elevated risk of venous thromboembolism,⁴¹ a recent population-based study of 5326 patients with MGUS found that 10 years after diagnosis, patients with MGUS were 2.1 times more likely to experience venous thrombosis and 1.3 times more likely to experience arterial thrombosis than matched control participants.⁴² In contrast to multiple myeloma, where risk of thrombosis is related to disease activity and therapy used,⁴³ this elevated risk did not correlate with M-protein concentration. Despite negative showings from a skeletal survey, fracture risk is elevated in MGUS. In the cohort of 5326 patients discussed previously and in another cohort of 488 patients, it was found that

patients with MGUS were more likely than matched control participants to develop fractures at any site and much more likely to develop multiple fractures, although risk of appendicular fractures was only about 30% greater compared with a 140% risk increase of pelvic/vertebral fractures.^{26,44} Neither thrombotic complications⁴² nor fractures⁴⁴ predicted progression to multiple myeloma, supporting the idea that hypercoagulability and osteoclastic activation occur early in the pathogenesis of plasma cell neoplasia rather than abruptly in early multiple myeloma. These findings suggest a need for randomized, prospective clinical studies aimed at developing prophylaxis for thrombosis and fractures among patients with MGUS, while minimizing the adverse events of such interventions.

For smoldering myeloma, the 2010 IMWG guidelines suggest an initial evaluation to confirm the diagnosis (SPEP, 24-hour urine with urine protein electrophoresis, and serum FLC) and rule out multiple myeloma (complete blood cell count, calcium, and creatinine) at baseline and at 2 to 3 months along with a baseline bone marrow biopsy and skeletal survey. Laboratory studies should be repeated at 4- to 6-month intervals for the first year, with lengthening of the follow-up interval to 6 to 12 months if stable.¹ As mentioned previously, MRI may help to detect small lesions and is recommended for patients with bone-related symptoms.^{1,36} No differential management based on risk stratification is suggested.

In accord with current guidelines, MGUS and smoldering myeloma should not be treated outside of clinical trials.¹ Treatment trials for MGUS are problematic, as patients are relatively healthy and most patients have a low lifetime risk of progression, especially when other causes of death are taken into account.⁹ Thus, an ideal treatment would be nontoxic and directed toward patients with high risk of progression.

Early treatment strategies for smoldering myeloma are particularly attractive as the rate of progression to multiple myeloma is quite high. Prior to the advent of novel therapies, a randomized controlled trial of melphalanprednisone (standard of care for multiple myeloma), initially or at progression to multiple myeloma, found no difference in response rate or overall survival.⁴⁵ A single-group trial using thalidomide and pamidronate in 76 patients with smoldering myeloma failed to show a clear benefit for treatment, with a shorter time to progression among responders than nonresponders, although more than 50% of patients discontinued therapy due to adverse events.⁴⁶ Another randomized trial (zoledronic acid vs surveillance) found reduced skeletal complications at progression without impact on progression.⁴⁷ A trial randomizing patients with high-risk smoldering myeloma to lenalidomide-dexamethasone vs active surveillance is ongoing. Interim analysis indicates that at 19 months of follow-up, approximately 50% of patients in the surveillance group progressed to multiple myeloma while almost no treated patients progressed.⁴⁸ However, it is unknown whether treating patients with smoldering myeloma improves overall survival or quality of life, as such data are not yet available.

While these recent 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 relatively benign maintenance therapy used to control the malignant clone. Alternately, highly active therapy could be used with the goal of cure, although this

may prove challenging in the context of current treatment options. However, to responsibly perform any such trial, well-designed correlative studies should be performed to assess the theoretical possibility of unexpected long-term adverse events or selecting for more aggressive disease.

FUTURE DIRECTIONS

Evaluation and management of cases of patients with myeloma precursor disease continues to prove challenging in the environment of expanded biological knowledge and limited high-level evidence. 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, one that must be approached via prospective clinical monitoring and extensive correlative science. In the future, these highest-risk patients with detectable disease on advanced imaging will likely become candidates for early treatment strategies, likely with agents not currently available in the clinic. However, such trials should be cautiously designed to assess progression-free and overall survival, as high response rates may not correlate with survival and prolonged stable disease may provide key benefit to patients.

Acknowledgments

Funding/Support: Research for this article was supported by the Intramural Research Program of the National Cancer Institute of the National Institutes of Health.

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Figure 1. Case Patient's M-Protein Levels Over Time

Diagnosis showed monoclonal gammopathy of undetermined significance (MGUS), and an M protein level that remained relatively stable for approximately 10 years before rapidly increasing in 2009.

^aBone marrow biopsy performed in November 2009.

^bBone pain reported in January 2010.

Figure 2. Case Patient's Bone Marrow Biopsy

The diagnosis of smoldering myeloma was determined from a bone marrow biopsy. A, Hematoxylin-eosin staining shows 30% to 50% marrow cellularity. B, Immunostaining for CD138 (brown chromagen; hematoxylin counterstain) shows 40% CD138+ cells. Based on the 2010 International Myeloma Working Group criteria,¹ CD138 staining of the marrow core is the reference standard for determining percentage of plasma cells. C and D, Immunostaining for free κ light chains (C) and free λ light chains (D) using a brown chromagen and hematoxylin counterstain shows a κ light chain restriction pattern with almost no λ -positive plasma cells. Immunohistochemistry for CD138 (B-A38; Cell Marque) and κ and λ light chains (DAKO, Carpinteria, California) was performed on Ventana using an Ultra View DAB detection kit (Ventana Medical Systems, Tucson, Arizona). CD138 staining of the marrow core was used as the criterion standard for determining percentage of plasma cells (original magnification $\times 100$ for all photomicrographs).

Figure 3. Immunophenotype Analysis of Case Patient's Bone Marrow Biopsy

A, Plasma cells were gated for analysis (indicated by blue border) based upon characteristically bright (increased) CD38 expression; plasma cell differentiation was further confirmed by the expression of CD138 in this population (C). By flow cytometry, 12% of cells were plasma cells compared with 40% plasma cells by immunohistochemistry. This much lower percentage of plasma cells was due to hemodilution, precluding the use of flow cytometry to quantitatively analyze the percentage of plasma cells. B and C, Antigen-negative populations are located in the 1-to-10 region of the scales. B, Analysis for κ and λ light chains demonstrated κ light-chain restriction. C, Almost all plasma cells were found to be immunophenotypically abnormal: CD38-positive, CD45-negative, CD19-negative, and dim (decreased) CD27 expression.

Figure 4. Case Patient's FDG PET/CT Studies of the Sacrum

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) showed metabolically active and anatomically visible lesions (arrowheads) in the sacrum (standard uptake value [SUV] 3.4) and the iliac bone (SUV 2.8).

Figure 5. Biological Events Related to Progression From Precursor Disease to Multiple Myeloma

The biological transition from normal plasma cells to multiple myeloma precursor disease (monoclonal gammopathy of undetermined significance [MGUS] and smoldering myeloma) to multiple myeloma consists of many overlapping oncogenic events. These events do not all occur in each affected individual, eg, hyperdiploidy is present in approximately 50% of precursor and multiple myeloma tumors. In this illustration, solid lines approximate the period during which the oncogenic event is likely to occur; dashed lines indicate less certainty in the timing. Once an oncogenic event occurs, it almost always persists. The 2 major types of early events include IgH translocations [most commonly: t(4;14), t(14;16), t(6;14), t(11;14), and t(14;20)] and hyperdiploidy, although most tumor cells have only 1 of these 2 events. Either of these can coexist with deletion of chromosome 13, although this abnormality most commonly (>80% to 90% of patients) occurs with the t(4;14), t(14;16), and t(14;20) IgH translocations.^{15,16} A unifying early event in most, perhaps all, precursor and multiple myeloma tumors is the dysregulation of a cyclin D gene. Secondary translocations, sometimes involving an Ig locus, can occur at any stage of myelomagenesis. Activating mutations of *NRAS* and *KRAS* are each present in about 15% of multiple myeloma tumors; *NRAS* mutations are present in MGUs tumors while *KRAS* mutations are absent from MGUS tumors. Constitutive activation of the nuclear factor κB (NFκB) pathway is mediated by mutations in some tumors during progression.¹⁷ Other events, such as Rb gene inactivation or deletion of p53 or p18 genes, are mostly seen at the level of advanced intramedullary or extramedullary multiple myeloma.^{15,18} Through the stage of

intramedullary multiple myeloma the tumor cells are strongly dependent on the bone marrow microenvironment.¹⁹ The reciprocal interaction of the bone marrow microenvironment and the tumor cells results in changes in the bone marrow microenvironment, which are responsible for the lytic lesions that are characteristic of multiple myeloma. Extramedullary tumor cells have developed features that make them independent of the bone marrow microenvironment.