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A Case Study Progression to Multiple Myeloma

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Abstract

Multiple myeloma consistently is preceded by precursor states, which often are diagnosed incidentally in the laboratory. This case report illustrates the clinical dilemma of progression from precursor to full malignancy. The article also discusses future directions in management and research focusing on myelomagenesis.

Multiple myeloma, characterized by the clonal proliferation of plasma cells in the bone marrow, is the second most common hematologic malignancy, with more than 20,000 new cases diagnosed per year in the United States (Laubach, Richardson, & Anderson, 2010). Typical clinical features include anemia, renal failure, hypercalcemia, and skeletal lytic lesions (Kyle & Rajkumar, 2004) (see Table 1). Despite significant advances in treatment, multiple myeloma has high morbidity and mortality reflected by an overall length of survival of about four to seven years (Kumar et al., 2008, Turesson, Velez, Kristinsson, & Landgren, 2009).

Multiple myeloma has two precursor states: monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma. MGUS is asymptomatic and affects about 3% of Caucasians older than age 50. MGUS has a 1% average annual risk for progression to multiple myeloma or related lymphoproliferative malignancies (Kyle et al., 2002, 2007) (see Figure 1). Two independent studies showed that multiple myeloma consistently is preceded by MGUS (Landgren et al., 2009; Weiss, Abadie, Verma, Howard, & Kuehl, 2009). Smoldering multiple myeloma is another asymptomatic precursor to multiple myeloma with a substantially higher annual risk of progression. Smoldering multiple myeloma is defined by a monoclonal-protein concentration of 3 g/dl or higher or 10% or higher bone marrow plasma cells in the absence of end-organ damage (International Myeloma Working Group, 2003). To date, an estimated 3,000 smoldering multiple myeloma

cases are diagnosed annually in the United States; however, the numbers likely are not reliable because of prior inconsistent diagnostic criteria and under diagnosis from the malignancy's asymptomatic nature (Rajkumar, Lacy, & Kyle, 2007). Based on retrospective data from the Mayo Clinic, the average annual risk of progression from smoldering multiple myeloma to multiple myeloma is 10% for the first five years following smoldering multiple myeloma diagnosis, decreasing to 3% annually for the following five years, and becoming the same 1% annual rate of progression as MGUS thereafter (Kyle et al., 2007).

Case Report

In the late 1990s, Mr. A, an otherwise healthy 65-year-old Caucasian man, underwent a regular health check-up. As part of the blood work, serum protein electrophoresis was conducted. During the work-up, a monoclonal protein was detected and confirmed with immunofixation electrophoresis. The monoclonal protein was defined as immunoglobulin-G kappa with a concentration of 1.25 g/dl; the quantitative uninvolved immunoglobulin levels all were found to be normal. In addition, the complete blood count revealed normal hemoglobin, calcium, and creatinine levels. Mr. A was diagnosed with MGUS. Given the features of the serum protein abnormalities, Mr. A was recommended to have annual follow-up appointments to monitor his blood work. For several years, his monoclonal-protein level stayed in the range of 1–2 g/dl and he did not have other laboratory abnormalities or symptoms.

In early 2009, Mr. A's monoclonal-protein level increased to 3.2 g/dl. He underwent a bone marrow biopsy with immunohistochemistry (CD138, kappa and lambda stains). Results of the biopsy showed 30%–40% plasma cells with kappa light-chain restriction. In addition, flow cytometry of the bone marrow aspirate showed that more than 99% of the plasma cells were abnormal. Serum calcium and creatinine levels were within normal limits. Albumin level was 3.2 g/dl, and the beta-2-microglobulin level was 2.3 mg/L. Skeletal survey was negative for lytic lesions. Taken together, the observations changed Mr. A's diagnosis from MGUS to smoldering multiple myeloma.

After diagnosis, Mr. A was monitored every two months and assessed with serum protein electrophoresis, immunofixation electrophoresis, and routine laboratory tests (including calcium, albumin, complete blood count, and creatinine). The monoclonal-protein concentration increased by 0.3–0.5 g/dl at each visit, whereas calcium levels gradually increased and hemoglobin gradually decreased, despite the absence of clear symptoms.

In late 2009, Mr. A reported diffuse back pain and unspecific weak pain from the pelvis, so magnetic resonance imaging was done to exclude spinal cord compression; the result was negative. An 18-F-fluoro-deoxy-2-glucose positron-emission tomography/computed tomography (18-FDG PET/CT) scan had been done in early 2009 when the monoclonal-protein levels started to increase; the examination showed suspicious lesions in the vertebrae, whereas the skeletal survey was negative. Another 18-FDG PET/CT scan was conducted to compare to the previously noted abnormalities in the vertebrae. The scan revealed low intensity focal lesions in the sacrum and left iliac bone consistent with lytic lesions; again, the skeletal survey was negative for lytic lesions. According to diagnostic

criteria, either lytic lesions or “abnormal compression fractures of vertebrae” detected by skeletal survey qualify for a diagnosis of multiple myeloma (International Myeloma Working Group, 2003). In the context of Mr. A’s increasingly abnormal laboratory values, increased focal lesions on PET/CT, and symptoms in the area of abnormality, he was interpreted biologically and clinically as having multiple myeloma. He then began treatment for multiple myeloma.

Progression to Multiple Myeloma

To date, predicting whether an individual patient with MGUS or smoldering multiple myeloma will ultimately progress to multiple myeloma is not possible. However, two schemas have been developed to help define patients at higher or lower than average risk of progression (see Tables 2 and 3). Using the results of serum-protein assays including quantity of monoclonal protein, type of immunoglobulin heavy chain, and serum-free light chain ratio, as well as percentage of bone marrow plasma cells by biopsy in smoldering multiple myeloma, the Mayo Clinic developed a scheme to stratify patients based on risk of progression to multiple myeloma (Dispenzieri et al., 2008; Rajkumar et al., 2005). The Spanish Programa Para el Estudio de la Terapéutica en Hemopatía Maligna (Program for the Study of Therapy in Hematologic Malignancies) (PETHEMA) study group developed a risk stratifications scheme based primarily on the results of immunophenotyping by flow cytometry, which requires a bone marrow aspirate sample (Perez-Persona et al., 2007). Mr. A was at the highest risk for progression to multiple myeloma by the PETHEMA scheme (95% or higher abnormal plasma cells and decreased uninvolved immunoglobulins) and intermediate risk for progression by the Mayo Clinic criteria (monoclonal protein 3 g/dl or higher, bone marrow plasma cells 10% or higher, but serum-free light chain ratio lower than 8).

Smoldering Multiple Myeloma

Although no formal guidelines exist for evaluation and follow-up, the Mayo Clinic recommends follow-up at two- to three-month intervals for the first year with monitoring of monoclonal-protein levels, serum chemistry, complete blood count, and urine protein studies (Blade, Dimopoulos, Rosinol, Rajkumar, & Kyle, 2010). After that time, follow-up intervals may be extended to up to six months and maintained or reduced based on the patient’s risk profile. Because of the heterogeneous prognosis, thoughtful patient education is critical at all visits.

Outside of clinical trials, patients with smoldering multiple myeloma should not be treated unless progression to multiple myeloma occurs (Kyle et al., 2007). Current guidelines do not endorse treatment of patients with smoldering multiple myeloma (Kyle et al., 2007). In fact, prior clinical trials have not shown an increase in overall survival for patients with smoldering multiple myeloma treated with melphalan-prednisone, thalidomide, or bisphosphonates, but zoledronate therapy decreased the risk of pathologic fractures following progression (Barlogie et al., 2008; Hjorth et al., 1993; Musto et al., 2008). Preliminary data from an ongoing phase III trial using lenalidomide-dexamethasone versus observation in high-risk smoldering multiple myeloma has shown lower risk of progression for patients

assigned to the treatment arm; overall survival data are not yet available (Mateos et al., 2009). The goal of treating smoldering multiple myeloma is to cure the disease outright or to manage it chronically, delaying progression to full myeloma and improving survival. However, clinicians should consider the possibilities of significant drug toxicities, development of refractory disease, and long-term adverse events in asymptomatic patients (Waxman, Kuehl, Balakumaran, Weiss, & Landgren, in press).

Conclusion

Multiple myeloma is a diagnosis based on clinical, laboratory, and radiographic assessment for myeloma-related end-organ damage. In contrast, MGUS and smoldering multiple myeloma often are incidental laboratory diagnoses based on presence and size of the monoclonal protein and percentage of bone marrow plasma cells. Current criteria for the diagnosis of MGUS, smoldering multiple myeloma, and multiple myeloma were developed by the International Myeloma Working Group in 2003. However, as in the case of Mr. A, the clinical picture can be highly complex, requiring very careful history and physical examination correlated with laboratory values and newer imaging studies.

Prospective molecular profiling studies are ongoing, with the expectation of gaining more accurate risk stratification for individuals with MGUS and smoldering multiple myeloma. Knowledge of present and future predictors of risk for progression may allow for better monitoring of patients with myeloma precursor disease. Future goals are to identify high-risk individuals and develop effective therapies with limited side effects aimed at delaying progression or cure in high-risk patients. At the National Institutes of Health in Bethesda, MD, ongoing studies focus on molecular profiling and the development of novel therapies for high-risk myeloma precursor disease. For more information, visit www.clinicaltrials.gov.

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Figure 1. Probability of Progression From Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma to Active Multiple Myeloma
Note. From “Clinical Course and Prognosis of Smoldering (Asymptomatic) Multiple Myeloma,” by R.A. Kyle, E.D. Remstein, T.M. Therneau, A. Dispenzieri, P.J. Kurtin, J.M. Hodnefield, and S.V. Rajkumar, 2007, *New England Journal of Medicine*, 356, p. 2582. Copyright 2007 by Massachusetts Medical Society. All rights reserved.

Table 1.**Diagnostic Criteria for Multiple Myeloma and Precursor States**

CRiTeRion	MGUS	SMM	MM
Monoclonal protein in serum	< 3 g/dl	3 g/dl	Any
Monoclonal plasma cells in bone marrow	< 10%	10%	Any
End-organ damage ^a	No	No	Yes

^aEnd-organ damage is defined as hypercalcemia (calcium higher than 11 mg/dl), anemia (hemoglobin lower than 10 g/dl), renal failure (standard creatinine higher than 1.95 mg/dl), and bone disease (lytic lesions by skeletal survey, osteoporosis with abnormal compression fractures, or spinal cord compression).

MGUS—monoclonal gammopathy of undetermined significance; MM—multiple myeloma; SMM—smoldering multiple myeloma

Note. From “Criteria for the Classification of Monoclonal Gammopathies, Multiple Myeloma and Related Disorders” by the International Myeloma Working Group, 2003, *British Journal of Haematology*, 121, pp. 752–753. Copyright 2003 by John Wiley and Sons. All rights reserved. Adapted with permission.

Table 2.**Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma: Predictors of Progression**

RISK FACTOR	MAYO CLINIC (%)^a	PETHEMA (%)^b
0	5	2
1	21	10
2	37	46
3	58	-

^aProgression was assessed at 20 years. Risk factors were monoclonal protein higher than 1.5 g/dl, immunoglobulin A or M monoclonal gammopathy of undetermined significance, and serum-free light chain ratio lower than 0.26 or higher than 1.65.

^bProgression was assessed at five years. Risk factors were 95% or higher abnormal plasma cells by flow cytometry and DNA aneuploidy by flow cytometry.

PETHEMA—Programa Para el Estudio de la Terapéutica en Hemopatía Maligna (Program for the Study of Therapy in Hematologic Malignancies)

Note. Based on information from Perez-Persona et al., 2007; Rajkumar et al., 2005.

Table 3.**Smoldering Multiple Myeloma to Multiple Myeloma: Predictors of Progression at Five Years**

RISK FACTOR	MAYO CLINIC (%)^a	PETHEMA (%)^b
0	-	4
1	25	46
2	51	72
3	76	-

^aRisk factors were bone marrow plasma cells of 10% or higher, monoclonal protein 3 g/dl or higher, and serum-free light chain ratio lower than 0.125 or higher than 8.

^bRisk factors were 95% or higher abnormal plasma cells by flow cytometry and reduction of uninvolved immunoglobulins.

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Note. Based on information from Dispenzieri et al., 2008;Perez-Persona et al., 2007.