

# A Case Study Progression to Multiple Myeloma

Mary Ann Yancey, RN, MSN, AOCN®, Adam J. Waxman, and Ola Landgren, MD, PhD

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

Mary Ann Yancey, RN, MSN, AOCN®, is a senior research nurse, Adam J. Waxman is a medical student, and Ola Landgren, MD, PhD, is a principal investigator, all in the Medical Oncology Branch at the Center for Cancer Research at the National Cancer Institute of the National Institutes of Health in Bethesda, MD.

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