

# How We Approach Smoldering Multiple Myeloma

Noopur Raje, MD<sup>1,2</sup> and Andrew J. Yee, MD<sup>1,2</sup>

*The Oncology Grand Rounds series is designed to place original reports published in the Journal into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in Journal of Clinical Oncology, to patients seen in their own clinical practice.*

## CASE PRESENTATION

A 54-year-old man was seen for smoldering multiple myeloma (SMM). Five years ago, a routine physical examination showed an elevated total protein level. Laboratory studies at that time revealed an immunoglobulin G (IgG) lambda monoclonal protein level of 2.39 g/dL, with a normal CBC and metabolic panel, consistent with monoclonal gammopathy of undetermined significance. Serum protein electrophoresis now shows a monoclonal protein level measuring 4.52 g/dL. Serum free lambda chains were elevated at 426.6 mg/L, with an elevated involved/uninvolved free light chain ratio of 40. A positron emission tomography (PET)-computed tomography (CT) scan did not show any evidence of bone disease. A bone marrow biopsy confirmed the presence of 26% clonal plasma cells, and fluorescence in situ hybridization (FISH) showed monosomy 13 and hyperdiploidy. The patient returns to discuss therapeutic options.

## CHALLENGES IN DIAGNOSIS AND MANAGEMENT

Monoclonal gammopathy of undetermined significance (MGUS) and SMM are precursor conditions for multiple myeloma (MM). MM is a malignancy of plasma cells traditionally defined by the presence of hypercalcemia, renal dysfunction, anemia, or bone lesions (the CRAB criteria). MGUS nearly always precedes the onset of MM.<sup>1,2</sup> Table 1 lists the diagnostic criteria for these plasma cell disorders.

SMM, initially described in 1980, occupies the middle space between MGUS and MM, with higher disease burden but without the clinical sequelae of the CRAB criteria or “myeloma” defining biomarkers.<sup>3</sup> SMM is less common than MGUS, representing an estimated 13.7% of patients with MM, with 4,100 new patients per year.<sup>4</sup> The rate of progression to active MM is 10% per year for the first 5 years, declines to 3% per year for the next 5 years, and is then 1% per year for the following 10 years. The cumulative probability of progression from SMM to MM is 73% at 15 years.<sup>5</sup> There is debate as to whether SMM is a condition to be treated as an early stage of MM<sup>6</sup> or simply observed, as with MGUS. To date, neither genomic sequencing

nor expression profiling have identified a molecular predictor for patients with SMM who progress to MM.<sup>7</sup> It is possible that factors independent of the myeloma cell, but related to the microenvironment, play a more important role in disease progression.<sup>8</sup>

In 2014, the International Myeloma Working Group (IMWG) expanded the definition of MM to include a category of myeloma-defining biomarkers: clonal bone marrow plasma cell percentage  $\geq$  60%, involved/uninvolved serum free light chain ratio  $\geq$  100, or  $>$  1 focal lesion on magnetic resonance imaging (MRI).<sup>9</sup> The motivation behind the biomarker definition was to identify asymptomatic patients with a high risk (80% or more) of developing a CRAB-related event within 2 years. Nearly 15% of patients previously considered to have SMM would be upstaged to active MM under the 2014 biomarker definition. Subsequent studies suggest that these criteria, such as the free light chain criteria, may not confer as high a risk as initially defined,<sup>10,11</sup> underscoring the challenges in predicting MM development.

The updated criteria emphasize the importance of imaging in SMM to carefully exclude myeloma-defining bone lesions. Conventional skeletal surveys are inadequate for this purpose, because a lytic lesion needs to involve more than 50% of the bone before it can be detected.<sup>12</sup> CT is more sensitive than plain radiographs, and whole-body CT protocols using lower doses of radiation have been evaluated. In one study, low-dose whole-body CT (LDWBCT) detected lytic lesions in 22.5% of patients with SMM and MM that were not visualized on conventional skeletal survey.<sup>13</sup> The IMWG recently recommended LDWBCT, and if negative, proceeding to whole-body MRI or spine and pelvis MRI.<sup>14</sup> PET-CT is an appropriate alternative to LDWBCT.

## Risk Stratification

Efforts to refine prognosis in SMM have examined additional risk factors for progression (Table 2), such as an increase in monoclonal protein (“evolving pattern”), decrease in hemoglobin, and immunoparesis (suppression of the uninvolved immunoglobulins).<sup>11,15-18</sup> Elevated circulating plasma cells,<sup>19</sup> atypical bone

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**TABLE 1.** Criteria for Diagnosis of MGUS, Smoldering Multiple Myeloma, and Multiple Myeloma

Criteria
<b>Non-IgM MGUS</b>
Serum monoclonal protein < 3 g/dL and
Clonal bone marrow plasma cells < 10% and
Absence of end-organ damage (CRAB criteria) or amyloidosis
Progression to multiple myeloma, solitary plasmacytoma, or AL amyloidosis: 1%/year
<b>IgM MGUS</b>
Serum IgM monoclonal protein < 3 g/dL and
Bone marrow lymphoplasmacytic infiltration < 10% and
No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the underlying lymphoproliferative disorder
Progression to Waldenström macroglobulinemia or AL amyloidosis: 1.5%/year
<b>Light chain MGUS</b>
Abnormal free light chain ratio with elevation in involved free light chain and
Negative immunofixation for immunoglobulin heavy chain and
Clonal bone marrow cells < 10% and
Urinary monoclonal protein < 500 mg/24 hours and
Absence of end-organ damage (CRAB criteria) or amyloidosis
Progression to light chain multiple myeloma or AL amyloidosis: 0.3%/year
<b>Smoldering multiple myeloma</b>
Serum monoclonal protein (IgG or IgA) $\geq$ 3 g/dL or 24-hour urine monoclonal protein $\geq$ 500 mg and/or clonal bone marrow plasma cells 10%-60% and
No myeloma-defining events (see below) or amyloidosis
<b>Multiple myeloma</b>
Clonal bone marrow plasma cells $\geq$ 10% or biopsy-proven plasmacytoma and
Myeloma-defining event:
End-organ damage (CRAB criteria) or
Biomarker of malignancy (one or more of the following)
Clonal bone marrow plasma cell percentage $\geq$ 60% or
Involved/uninvolved free chain ratio $\geq$ 100 with involved free light chain $\geq$ 100 mg/L or
> 1 focal lesion on MRI ( $\geq$ 5 mm)

NOTE. End-organ damage (CRAB criteria) includes the following: Hypercalcemia, calcium > 1 mg/dL higher than the upper limit of normal or > 11 mg/dL; or renal insufficiency, creatinine clearance < 40 mL/min or creatinine > 2 mg/dL; or anemia, hemoglobin > 2 g/dL below the lower limit of normal or hemoglobin < 10 g/dL; or bone lesions, one or more osteolytic lesions on skeletal radiography or CT. See also Rajkumar et al.<sup>9</sup>

Abbreviations: AL, amyloid light chain; CRAB, hypercalcemia, renal dysfunction, anemia, or bone lesions; CT, computed tomography; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging.

marrow plasma cells defined by flow cytometry,<sup>17</sup> and certain FISH abnormalities, such as t(4;14) and deletion 17p, are more risk factors to consider,<sup>20</sup> but these measures were

developed before the 2014 update in the MM criteria, and the specialized flow cytometry methods are not widely available.

To address the updated definition of SMM, the Mayo group revised their risk stratification (Table 2).<sup>21</sup> They identified 3 risk factors for progression (20/2/20): bone marrow plasma cell involvement > 20%, monoclonal protein > 2 g/dL, and free light chain ratio > 20. The study defined 3 groups—low risk (no risk factors), intermediate risk (1 risk factor), and high risk (2 or more risk factors)—where the risk for progression at 2 years was 9.7%, 26.3%, and 47.4%, respectively, and this improved stratification compared with the previous Mayo 2008 model.<sup>22</sup> The IMWG validated the 20/2/20 model in a separate cohort of more than 1,000 patients, showing a 2-year progression risk of 5%, 17%, and 46% for the same groups.<sup>23</sup> Incorporating chromosomal abnormalities identified by FISH found that the presence of t(4;14), t(14;16), 1q gain, or deletion 13q were additional risk factors. In patients with 3 or more risk factors, the risk of progression at 2 years was 59%.<sup>23</sup>

The IMWG recommends follow-up 3 months after the initial SMM diagnosis, and if the results are stable, follow-up should be every 4-6 months for a year, and then every 6-12 months.<sup>24</sup> Imaging with, for example, MRI should also be performed on an annual basis for at least 5 years.<sup>14</sup> Beyond 5 years, the risk of progression in all 3 groups studied in the 20/2/20 model stabilized at 3%-5% per year.<sup>21</sup>

An assumption with all of these models is that there is an inherent relationship between plasma cell burden and progression and that progression is a linear process.<sup>25</sup> However, an insight from whole-genome sequencing of paired samples at the time of SMM diagnosis and progression suggests that progression is not always linear.<sup>26</sup> In this study, 2 different patterns of progression were identified, a “static progression model,” where progression reflected accumulation of disease burden, versus the “spontaneous evolution model,” where an additional change drove a proliferative advantage. In support of these patterns is an analysis of a screening study conducted by the National Cancer Institute across multiple tumor types that analyzed serial serum samples of patients before developing MM.<sup>27</sup> Interestingly, the study found a group of patients (37.2%) who eventually developed MM, who progressed from low-risk or intermediate-risk to high-risk MGUS within only 5 years, suggesting that risk for progression may be more dynamic than previously modeled. Moreover, the study identified a proportion (although small) of patients who progressed from low-risk MGUS directly to MM, which suggests the spontaneous evolution model.

## SUMMARY OF THE RELEVANT LITERATURE

### Initial Studies

After the initial description of SMM in 1980, several trials investigated whether early initiation of treatment could

**TABLE 2.** Risk Stratification Models for Smoldering Multiple Myeloma

Model	Risk Stratification (No. of risk factors)	Progression Rate, No. of years (%)	Median Time to Progression
Mayo 2007 <sup>5</sup>	Monoclonal protein only	5 (15)	228 months
Bone marrow plasma cells $\geq$ 10%	Bone marrow only	5 (43)	93 months
Monoclonal protein $\geq$ 3 g/dL	All 2	5 (69)	27 months
Mayo 2008 <sup>22</sup>			
Bone marrow plasma cells $\geq$ 10%	1	2 (12); 5 (25)	10 years
Monoclonal protein $\geq$ 3 g/dL	2	2 (27); 5 (51)	5.1 years
Free light chain ratio $>$ 8	3	2 (52); 5 (76)	1.9 years
PETHEMA <sup>17</sup>	None	5 (4)	Not reached
$\geq$ 95% phenotypically aberrant plasma cells in bone marrow	1	5 (46)	73 months
Immunoparesis	2	5 (72)	23 months
Mayo 2018 (20/2/20) <sup>21</sup>			
Bone marrow plasma cells $>$ 20%	None	2 (9.7); 5 (22.5)	109.8 months
Monoclonal protein $>$ 2 g/dL	1	2 (26.3); 5 (46.7)	67.8 months
Free light chain ratio $>$ 20	2	2 (47.4); 5 (81.5)	29.2 months

NOTE. Free light chain ratio is defined as involved/uninvolved serum free light chain. Immunoparesis is reduction below the lower limit of normal in the levels of 1 or 2 of the uninvolved immunoglobulins.

delay disease progression. The results of randomized trials comparing observation with melphalan and prednisone,<sup>28,29</sup> bisphosphonates,<sup>30,31</sup> and thalidomide<sup>32-34</sup> showed no clinically meaningful benefit for treatment compared with observation alone.

#### QuiRedex: Randomized Trial of Lenalidomide and Dexamethasone Versus Observation

The question of treatment of SMM was revisited with lenalidomide in the Spanish Myeloma Group randomized study, QuiRedex, comparing lenalidomide and dexamethasone versus observation in patients with high-risk SMM.<sup>35</sup> High-risk SMM was defined as (1) bone marrow involvement  $\geq$  10% and amount of monoclonal protein ( $\geq$  3 g/dL monoclonal IgG protein;  $\geq$  2 g/dL monoclonal IgA protein; or  $>$  1 g of urine Bence Jones protein/24 hours), or (2) one of these 2 criteria and  $\geq$  95% abnormal bone marrow plasma cells by flow cytometry and immunoparesis ( $>$  25% reduction in 1 or more uninvolved immunoglobulins). Time to progression was the primary endpoint, defined as time to developing symptomatic disease with the CRAB criteria. In the intervention arm, patients received lenalidomide 25 mg and weekly dexamethasone for 9 cycles, followed by maintenance lenalidomide 10 mg for 2 years. The study randomly assigned 119 patients. The overall response rate in the treatment arm was 79%, which deepened to 90% in the maintenance phase. Patients in the intervention arm had significantly longer time to progression, with the median not reached, versus 23 months in the observation arm in the updated analysis (hazard ratio [HR], 0.24; 95% CI, 0.14 to 0.41).<sup>36</sup> Significantly, early

intervention improved overall survival (OS), with 18% deaths in the treatment arm versus 36% in the observation group and an HR of 0.43 (95% CI, 0.21 to 0.92).

Although this study showed improvement in OS, it brought into focus several limitations in the diagnosis and follow-up of SMM. Assessment for bone disease was limited to skeletal survey, reflecting the standard practice at that time. Progression events occurred early in the observation arm, raising the possibility that some of these patients may have actually had active MM. Progression was mostly in the way of bone disease and renal failure, prompting the updated 2014 criteria incorporating improved imaging and serum free light chain ratio to define active MM.<sup>9</sup> These patients would likely now be reclassified as active MM and therefore excluded from the trial based on the updated 2014 criteria. Only 11% of patients in the observation arm who experienced disease progression were treated with lenalidomide (reflecting its limited availability at the time), which likely accounted for differences in OS.

#### E3A06: Randomized Trial of Lenalidomide Versus Observation

In this issue of *Journal of Clinical Oncology*, the Eastern Cooperative Oncology Group (ECOG) presents a larger randomized study, E3A06, of lenalidomide versus observation in SMM, using lenalidomide as a single agent without dexamethasone to isolate the contribution of lenalidomide without the adverse events associated with corticosteroids.<sup>37</sup> Patients with SMM by bone marrow involvement and abnormal free light chain ratio were eligible to participate. This study started enrolling patients in February

2013, before the updated 2014 definition of SMM, and the majority of patients satisfied the updated definition with exclusion of myeloma-defining events. Compared with previous studies, evaluation for bone involvement was more rigorous because the trial required MRI of the spine and the pelvis. The primary endpoint was progression-free survival (PFS), where progression was defined by the presence of both biochemical disease progression as defined by the IMWG and evidence of end-organ damage by the traditional CRAB criteria.

The study randomly assigned 182 patients between February 2013 and July 2017 to lenalidomide 25 mg on the conventional 21-out-of-28-days schedule versus observation. The overall response was 50% in the treatment arm. The PFS was longer in the lenalidomide arm, with an HR of 0.28 (95% CI, 0.12 to 0.62) and 3-year PFS of 91% versus 66%. Of note, the PFS in the observation arm was better than the observation arm of the Spanish trial, where the median PFS was 23 months. This likely reflects the fact that patients in the ECOG study may be more representative of an SMM population, under the current definition. Although the number of patients in the individual cohorts is small, the improvement in PFS is best demonstrated in the 20/2/20 high-risk category, with an HR of 0.09 ( $n = 56$ ) and less so with the other risk cohorts. Bone progression was the basis for progression in most of the patients in the observation arm (11 of 21 patients with disease progression), even though all patients underwent screening spine and pelvis MRI, followed by anemia (8 of 21 patients). It would be relevant to know whether these progression events were associated with symptoms. Delaying an asymptomatic decrease in hemoglobin or appearance of an asymptomatic lucency on routine skeletal survey with lenalidomide may not be as clinically meaningful as preventing a symptomatic bone lesion. There were 2 deaths in the lenalidomide arm versus 4 deaths in the observation arm (the cause of death is not reported). No difference in OS has been observed to date. There were 14% grade 3-4 neutropenia events in the treatment arm, along with 20.5% grade 3 infections in the treatment arm; adverse events in the control arm were not captured. There were 4.5% invasive second primary cancers in the treatment arm versus 2.3% in the control arm. Eighteen of 90 patients (20%) discontinued treatment because of adverse events, and 80% of patients had a dose reduction.

The improvement in PFS is notable, especially in preventing bony events, which can be a significant cause of morbidity, although we do not know whether these events were symptomatic. Moreover, this benefit is seen without necessarily achieving a deep response, and even with the dose reductions and limited duration of treatment, important questions regarding dose and duration of treatment in this SMM population remain.

On the screening spine and pelvis MRI, nearly half of patients (47.2%) had an abnormality present (the specifics

are not reported currently). Although plasmacytomas were an exclusion in the protocol, it would be of interest to know whether any of these MRI abnormalities could be considered myeloma-defining events under the 2014 diagnostic criteria, whether there were differences in progression and the type of progression based on the MRI findings, and whether lenalidomide made a difference. Similarly, a small proportion of patients had myeloma-defining biomarkers with the 2014 criteria: 3.3% had bone marrow plasma cells  $\geq 60\%$ , and 8.2% had free light chain ratio  $> 100$  of 8.2%. If the analyses were repeated without these ultra-high-risk patients, does the magnitude of the benefit change?

Because patients with SMM are, by definition, asymptomatic, it is critical to weigh the impact of lenalidomide treatment on adverse effects and quality of life. Moreover, although the reported quality of life was similar between both arms, 51% of patients in the lenalidomide arm discontinued treatment, and 40% of the discontinuations were for adverse events. Ultimately, the best case for early initiation of treatment is demonstration of an OS benefit (which is not known at this time) and reduction in myeloma-related deaths.

### Ongoing Studies and Approaches

Although the ECOG E3A06 study makes a case for single-agent lenalidomide as “prevention,” at the other end of the spectrum is a more intensive approach, with the hypothesis that SMM represents the best opportunity for a potentially “curative” approach by achieving a deep response and where there is a potentially lower mutational burden that may be more treatment responsive.<sup>38</sup> There are several trials evaluating intensive regimens: carfilzomib, lenalidomide, and dexamethasone (KRd)<sup>39</sup>; KRd with high-dose melphalan and autologous stem-cell transplantation (GEM-CESAR)<sup>40</sup>; as well as the regimen in the ASCENT trial (ClinicalTrials.gov identifier: [NCT03289299](https://clinicaltrials.gov/ct2/show/study/NCT03289299)), which combines daratumumab with KRd. Additional combinations include elotuzumab with lenalidomide and dexamethasone<sup>41</sup> and lenalidomide, ixazomib, and dexamethasone.<sup>42</sup> The CENTAURUS study (ClinicalTrials.gov identifier: [NCT02960555](https://clinicaltrials.gov/ct2/show/study/NCT02960555)) evaluated daratumumab with different durations of treatment,<sup>43</sup> and there is also an ongoing study of isatuximab in high-risk SMM. The AQUILA study (ClinicalTrials.gov identifier: [NCT03301220](https://clinicaltrials.gov/ct2/show/study/NCT03301220)) is evaluating subcutaneous daratumumab (for up to 3 years) versus observation in high-risk SMM. Finally, there are therapies that more directly engage the immune system. This includes efforts with pembrolizumab<sup>44</sup> and myeloma peptide vaccination with PVX-410 and lenalidomide<sup>45</sup> and both with the selective HDAC6 inhibitor citarinstat (ClinicalTrials.gov identifier: [NCT02886065](https://clinicaltrials.gov/ct2/show/study/NCT02886065)).

To better answer the question of prevention versus treatment, ECOG has recently started a study comparing daratumumab, lenalidomide, and dexamethasone with



lenalidomide and dexamethasone, with OS as the primary outcome (ClinicalTrials.gov identifier: [NCT03937635](#)). Interestingly, their control arm includes dexamethasone, despite the current trial demonstrating the benefits of single-agent lenalidomide. The HOVON group (Haemato Oncology Foundation for Adults in the Netherlands) is conducting a similar study with carfilzomib and compares carfilzomib, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in high-risk SMM (ClinicalTrials.gov identifier: [NCT03673826](#)).

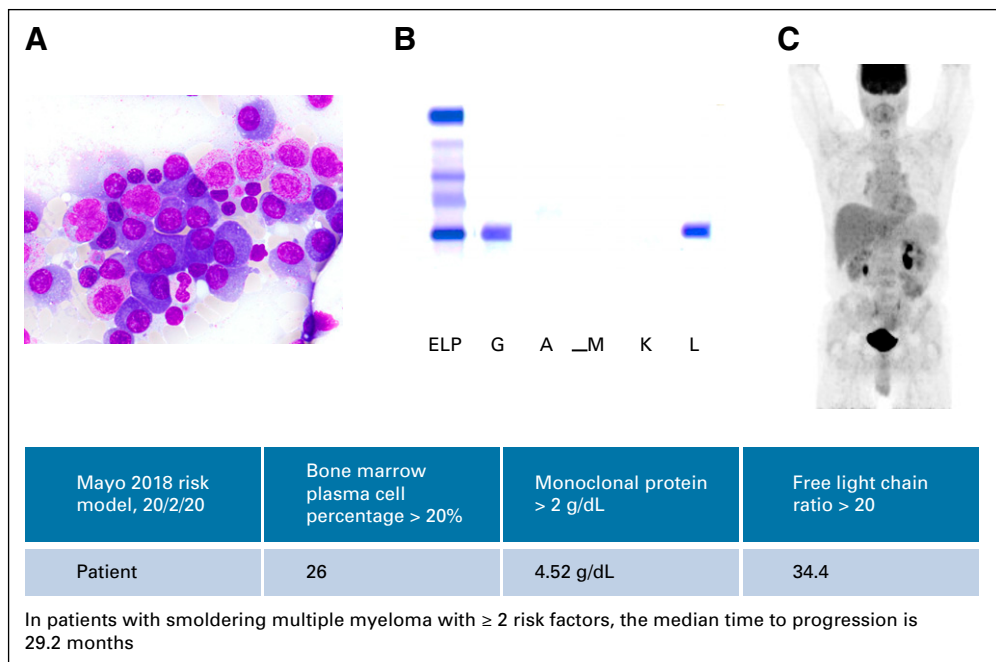
**SUGGESTED APPROACHES TO MANAGEMENT**

Management of a patient with SMM is challenging because the current risk stratification models do not allow us to accurately predict the risk of progression to active disease. Nevertheless, some important tools that can be used in the clinic now are the updated risk stratification with the 20/2/20 criteria, as well as advanced imaging with LDWBCT, MRI, and/or PET-CT. Ongoing studies to identify predictive biomarkers to further refine risk prediction will help select patients who may do well with observation.

The decision to treat is straightforward for patients with classic presentations of MM, such as painful bone lesions. The updated definition in 2014 now recommends treatment of asymptomatic patients who have a high risk of progression based on myeloma-defining biomarkers. Because more effective, better-tolerated treatments for MM

are now in use, it is only natural to evaluate these treatments earlier in the course of the disease, as in the case of SMM. The study by Lonial et al<sup>37</sup> potentially expands the eligibility for treatment to include patients with high-risk SMM, given the improvement in delaying symptomatic progression. Moreover, it argues for a fixed duration of lenalidomide as a single agent. Perhaps this represents a reasonable approach for this asymptomatic and otherwise well population rather than necessarily committing these patients to intensive and then prolonged treatment with maintenance therapy. However, for this asymptomatic population, the burden of proof justifying a change from observation is high.

At this time, we believe that close observation remains the standard of practice, although the current study may make the case for intervention in select patients with high-risk SMM. We maintain that the best endpoint for such studies should be OS or improvement in quality of life. We await mature results on OS from this trial and ongoing trials, as well as correlative studies to determine who benefits the most from early initiation of treatment, as well as from which treatment. While awaiting demonstration of such clinical gains, we need to be circumspect before broadly treating high-risk SMM. We hope that, ultimately, our understanding of plasma cell disorders will evolve and reclassify the patients in the SMM category as either patients who have MGUS and who may be observed versus patients who have “early” MM and who should be treated.



**FIG 1.** (A) Bone marrow aspirate, (B) serum protein electrophoresis (SPEP) and immunofixation, and (C) positron emission tomography–computed tomography (PET-CT) from a patient with smoldering multiple myeloma. The SPEP and immunofixation show an immunoglobulin G lambda monoclonal protein measuring 4.52 g/dL. The bone marrow aspirate had 26% plasma cells. PET-CT was negative for [<sup>18</sup>F]fluorodeoxyglucose-avid bone lesions. By the 20/2/20 criteria, this patient has high-risk smoldering multiple myeloma.

Based on the bone marrow involvement and level of monoclonal protein, our patient was classified as having SMM (Fig 1). There was no evidence of anemia, hypercalcemia, or bone lesions, and renal function was normal and unchanged; hence, he does not have MM. The new

Mayo 20/2/20 criteria stratify him in the high-risk SMM category, the group that gained the most in the ECOG E3A06 trial. Our patient chose to be observed, and 7 years after initial presentation, he continues under surveillance, with persistent disease classified as SMM.

## AFFILIATIONS

<sup>1</sup>Harvard Medical School, Boston, MA

<sup>2</sup>Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, Boston, MA

## CORRESPONDING AUTHOR

Noopur Raje, MD, Massachusetts General Hospital Cancer Center, 55 Fruit St, Boston, MA 02114; e-mail: nraje@partners.org.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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## AUTHOR CONTRIBUTIONS

**Conception and design:** All authors

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## **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

### **How We Approach Smoldering Multiple Myeloma**

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#### **Andrew J. Yee**

**Honoraria:** Amgen, Celgene

**Consulting or Advisory Role:** Takeda, Dexcel Pharma, Adaptive Biotechnologies, Celgene, Janssen, Karyopharm Therapeutics, Bristol-Myers Squibb, Amgen

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#### **Noopur Raje**

**Consulting or Advisory Role:** Amgen, Bluebird Bio, BMS, Celgene, Janssen