Is This Multiple Myeloma?

Parameswaran Hari, MD

The Patient:

A 57 yr old woman (NB) presented to her primary care doctor for a routine annual visit and physical. A CBC and chemistry panel were obtained during her evaluation and showed an elevated total protein level of 9.3 g/dL. Further work up including serum protein electrophoresis (SPEP) and immunofixation (IFE) indicated the presence of an IgG lambda monoclonal spike (M spike) of 2.52 g/dL. As a reminder, the diagnostic work-up required for multiple myeloma as well as tests that are useful under certain circumstances can be found in table 1.a and 1.b, respectively as listed in the NCCN Guidelines for multiple myeloma.

1a. Initial Diagnostic Workup for Multiple Myeloma – *Required*	
History and Physical	Serum quantitative immunoglobulins
CBC, differential & platelet count	Serum protein electrophoresis (SPEP)
BUN	Serum immunofixation electrophoresis (SIFE)
Creatinine	24-h urine for total protein
Electrolytes	Urine protein electrophoresis (UPEP)
Calcium	Urine immunofixation electrophoresis (UIFE)
Lactate dehydrogenase (LDH)	Skeletal survey
Beta-2 microglobulin	Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
Albumin	Cytogenetics
Serum free light chain assay	Fluorescence in situ hybridization (FISH) [del 13, del 17p13,t(4;14), t(11;14), t(14;16), 1q21 amplification]

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1b. Initial Diagnostic Workup for Multiple Myeloma – *Useful Under Some Circumstances*
MRI for suspected vertebral compression
CT scan (*avoid contrast*)
PET/CT scan
Tissue biopsy to diagnose solitary osseous or extraosseous plasmacytoma
Bone densitometry
Plasma cell labeling index
Staining of marrow and fat pad for amyloid
Serum viscosity
HLA typing

Baseline Results in 2007:

Hemoglobin was 13.2 g/dL, with hematocrit 39%. Platelets were 287 k/µL. White cell count was 11,000 µL, with a normal differential. The patient's calcium was 9.5 mg/dL, creatinine 0.7 mg/dL. Beta2 microglobulin levels were 2 mg/mL. Albumin was 3.6 g/dL (see table 2a).

Bone marrow aspirate and biopsy showed a marrow plasmacytosis of 30% against an overall background of normal to mildly increased marrow cellularity, myeloid and erythroid precursors were unremarkable. Overall plasmacytosis was estimated at 30% after CD138 staining. Flow cytometry showed the presence of CD56 positive, CD19 negative, lambda light chain restricted plasma cells.

Metastatic bone survey: NO evidence of osteolytic or osteoblastic bone lesions.

IgG levels were 4075 mg/dL. IgA and IgM were 63 mg/dL and 61 mg/dL respectively. Repeat protein electrophoresis confirmed a 2.77 g/dL M-spike consisting of IgG lambda (see table 2b). Urine protein electrophoresis positive for small faint IgG lambda excretion by immunofixation.

Cytogenetics and myeloma specific FISH studies were performed on the bone marrow biopsy showed a normal karyotype and 4.5% cells with monosomy 13 abnormality by FISH alone.

Patient denied any symptoms and specifically had no constitutional, neuropathic or infection related issues. She had been worked up for a high ESR 2 years prior and no obvious cause was discovered. Other concomitant medical problems included hyperlipidemia and degenerative joint disease.

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Table 2a. Laboratory Values

Lab/Normal Reference Range	Value
WBC 3.0–11.0 k/µL	11
Plt Ct 150–400 k/µL	287
Hgb 13.0–17.0 g/dL	13.2
Hct 39.0–51.0%	39
MCV 80–100 fL	98
RDW-CV 11.5–15.0%	12
Neut % 38.5–75.0%	58
Abs Neut 1.00–7.50 k/µL	6.38

Lab/Normal Reference Range	Value
BUN 8–25 mg/dL	14
Creatinine 0.7–1.4 mg/dL	0.7
Calcium 8.5–10.5 mg/dL	9.5
Albumin 3.5–5.0 g/dL	3.6
Beta 2 microglobulin 1.21-2.70 mg/mL	2.0
Alk Phos 40–150 U/L	108

(H)=high, (L)=low, WBC = white blood cell, Plt Ct = platelet count, Hgb = hemoglobin, Hct= hematocrit, MCV = mean corpuscular volume, RDW-CV = red cell distribution width–coefficient variation, Neut = neutrophils, Abs Neut = absolute neutrophils, BUN = blood urea nitrogen, Alk Phos = alkaline phosphatase

Table 2b. Laboratory Values (cont.)

SPEP: Lab/Normal Reference Range	Value
Immune Fixation	IgG Lambda Monoclonal peak
M-Spike (g/dL)	**2.77**

Lab/Normal Reference Range	Value
Serum IgG 717–1,411 mg/dL	**4,075 mg/dl**
Serum IgA 78–391 mg/dL	63
Serum IgM 53–334 mg/dL	61
FREE KAPPA *3.30 - 19.40 mg/L*	8.15
FREE LAMBDA *5.71 - 26.30 mg/L*	57.46

Gamma Glob = gamma globulin,

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Questions for the clinician:

Does my patient have Multiple Myeloma, Smoldering (Asymptomatic) Myeloma or Monoclonal Gammopathy of undetermined significance (MGUS)?

The most widely followed classification of plasma cell disorders is the IMWG schema from 2003 and 2010 which divided the spectrum of clonal PC disorders into MGUS, SMM and symptomatic MM. This classification is based on the overall disease burden and the presence of symptoms or signs of organ injury attributable to clonal PCs.

Multiple Myeloma requiring treatment (or active MM or symptomatic MM) is diagnosed based on the presence of PC related end-organ damage in the setting of laboratory evidence of a clonal PC process (M-protein and or monoclonal PC). End-organ damage in plasma cell disorders is indicated by hypercalcemia, renal insufficiency, anemia, bone lesions (the so called “CRAB” criteria). It is well recognized that other types of end organ damage (such as severe osteoporosis, neuropathy, amyloidosis, recurrent infections and hyperviscosity) can sometimes be attributed to clonal PCs. Table 3 summarizes the most recent definition of end organ damage from IMWG 2010 and NCCN criteria.

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Table 3. Previous and Updated Definitions of MGUS, Smoldering and Symptomatic Myeloma		
	IMWG and/or Previous NCCN Guidelines® Criteria [2,13,28]	**Updated Criteria: NCCN Guidelines® Version 2.2014 (released 11/8/2013)[4]**
Monoclonal gammopathy of undetermined significance (MGUS)	Serum M protein ≥ 3 g/dL ***AND*** < 10% bone marrow plasma cells ***AND*** No CRAB criteria	N/A
Smoldering (Asymptomatic) Myeloma[1]	Serum M protein ≥ 3 g/dL ***AND/OR*** ≥10% bone marrow plasma cells ***AND*** No CRAB criteria	M-Protein in serum -IgG ≥3 g/dL; -IgA >1 g/dL ***OR*** Bence-Jones protein > 1 g/24hr ***AND/OR*** Bone marrow clonal plasma cells ≥10% ***AND*** No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms. [No CRAB]
Active (symptomatic) Myeloma[2]	M protein in serum and/or urine ***AND*** ≥10% bone marrow plasma cells or plasmacytoma ***AND*** Presence of any CRAB criteria	Any one of the requirements satisfying the criteria for smoldering (asymptomatic) myeloma as described above be present ***AND*** Requires one or more of the following CRAB criteria: Calcium elevation (> 11.5 mg/dL) [> 2.65 mmol/L] Renal insufficiency (creatinine > 2 mg/dL) [≥ 177 µmol/L] Anemia (hemoglobin < 10 g/dL or 2 g/dL < normal) [< 12.5 mmol/L < normal] Bone disease (lytic or osteopenic) ***or*** See additional examples of active disease in Footnote 2
CRAB = Calcium elevation, renal insufficiency, anemia, bone lesions.		
NCCN (version 2.2014) provides the following important footnotes: 1. The understanding of SM is evolving rapidly. Some studies have shown that patients with certain characteristics including IgG levels of >3 g/dL, IgA of >2 g/dL, or urinary Bence Jones protein of >1 g/24 hours[18] or abnormal free light chain ratios,[5] have an increased risk of progression to active MM. It is also increasingly recognized, that the classical definition of SM using certain tests such as plain X-rays is outdated. Efforts to modify these criteria and reclassify some patients previously classified as "asymptomatic" to having "active disease" are underway. 2. Other examples of active disease include: repeated infections, amyloidosis, or hyperviscosity.		

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The pre MM states of MGUS and SMM are defined on laboratory criteria and the absence of end organ damage. Smoldering (asymptomatic) multiple myeloma is characterized by an M protein level of ≥ 3 g/dl or a clonal marrow plasmacytosis of ≥ 10% with no evidence of end-organ damage attributable to PC proliferation. MGUS is defined by an M protein <3 g/dl, <10% clonal PCs in the bone marrow (BM) and the absence of end-organ damage.

Based on these criteria, the patient in question carries a diagnosis of SMM. The key management issues in this scenario are 1) identifying MM precursor disease states vs. MM needing treatment based on clinical, laboratory and imaging criteria 2) defining risk of progression in those with MM precursor states 3) identifying pts who might benefit from early treatment 4) defining a follow up schedule. Emerging data and biological insights have raised the possibility of identifying those at the highest risk for imminent progression or might benefit from early treatment (while still not meeting current definitions of end organ damage criteria).

End Organ Damage and Limitations of CRAB criteria:

Since the differentiation between SMM and MM relies entirely on the detection of end-organ damage, detailed multidisciplinary clinical assessment is critical in addition to CBC, chemistry and traditional skeletal X-rays. The clinician's responsibility to exclude impending problems and stratify risk is greater in patients with SMM who do not receive therapy. Detection of early skeletal involvement is especially difficult

Modern imaging such as low dose CT bone scans, MRI scans or functional imaging with PET-CT or PET-MRI may detect bone damage earlier in the disease course. Among SMM patients with no bone lesions on skeletal X-rays up to 50% may have bony abnormalities on MRI of the lower spine. Whole body MRI techniques offer an overview of BM disease burden and specific patterns of marrow involvement (diffuse vs. focal). It has been reported that SMM patients with ≥2 focal bone lesions on MRI have a shorter median time to symptomatic MM. Similarly up to a third of SMM pts may have a diffuse pattern of marrow involvement comparable to MM pts. It is important to recognize that lack of insurance coverage, specialized radiologic expertise and implantable devices in patients may limit wide spread use of WB-MRI. PET-CT may be superior with regard to many of these limitations and is especially useful in excluding active MM.

Natural History and the risk of progression to MM:

Long term follow up data from the Mayo group suggest that the natural history and long term cumulative progression rate of SMM is about 10% per year for the first 5 years following diagnosis, thereafter reducing to 3% per year for the next 5 years and 1% per year for the remainder who have had no progression at 10 years. Thus the lowest risk end of the SMM spectrum consists of a significant proportion of patients (more than 20%) with a risk profile similar to that of MGUS. Thus SMM is best thought of as a heterogeneous grey area between MGUS and active MM. Majority of patients with SMM are in a pre-MM state, eventually progressing to therapy (as opposed to MGUS where the annual progression rate is 1%).

Some of highest risk patients in currently defined SMM state may have annual progression rates up to 40% (based on a variety of risk factors) and survival rates similar to those with symptomatic myeloma. Numerous risk factors and different schema have been proposed. Some of the risk factors used in

various schema for SMM progression models include: IgA isotype, involved FLC >8 times that of uninvolved FLC, circulating plasma cells detected by immunofluorescence, high plasma cell proliferation index, suppression of uninvolved immunoglobulin subtypes and a high fraction PCs with aberrancy. Should the highest risk SMM pts be reclassified as active MM or considered candidates for treatment in order to reduce imminent morbidity and avoid unnecessary treatment delay?

Early intervention strategies entail the risk of unnecessary therapy and side effects and the benefits of any such strategy depends on the validity of the risk stratification scheme. On the one hand, for those with ≥60% BM PCs at diagnosis, the median time to progression was 7 months and almost all of them (95%) progressed to MM eventually. It is very reasonable to reclassify this group (≥60% PCs) in the category of MM requiring treatment.

Identifying SMM patients with high risk of progression to MM:

The Mayo Clinic group has proposed a model that includes 1 point each for each of the following risk factors: M-protein level ≥3 g/dL, BM PCs ≥10%, and an FLC ratio (of < 0.125 or >8). The risk of progression to active MM at 5 years was 25%, 51%, and 76% those with 1, 2 or 3 risk factors respectively. A model developed by the Spanish PETHEMA group uses ≥ 95% aberrant BM PC (CD19 negative and/or CD45 expression, CD56 positivity, or weak CD38) detected by flow cytometry and uninvolved immunoglobulin suppression as independent risk factors. Progression rates at 5 years were 4%, 46%, and 72% for those with 0,1 or 2 risk factors, respectively. Concordance in risk assignment between the 2 models was found to be low in a recent study by NIH group. Models incorporating gene expression profiling (GEP) and proteomic profiling have also been proposed. The 2 most common models are compared in Table 4.

Table 4. Differences in Clinical Eligibility Criteria used for High-risk SM Trials

PETHEMA-GEM[18]	Eastern Cooperative Oncology Group (ECOG) E3A06[21,22]
1.) Bone marrow infiltration with plasma cells ≥ 10% ***AND*** 2.) Presence of a monoclonal component (ie, IgG ≥ 3 g/dL or IgA ≥ 2 g/dL or Bence-Jones proteinuria > 1 g/24 hours ***AND*** 3.) Absence of all of the following: lytic lesions; hypercalcemia; renal failure (creatinine ≥ 2 mg/dL); and anemia (hemoglobin < 10 g/dL or 2 g/dL below the lower normal limit). ***OR*** Patients with #1 ***OR*** #2 above, ***AND*** #3 could be included if patients met the following additional criteria: • At least 95% phenotypically aberrant plasma cells within the bone marrow plasma cell compartment ***AND*** Immunoparesis, defined as a reduction in the levels of 1 or 2 immunoglobulins of more than 25% in comparison to normal values	All of the following: • Bone marrow plasmacytosis with ≥ 10% plasma cells or sheets of plasma cells; marrow must be obtained by bone marrow aspiration and/or biopsy within 4 weeks prior to randomization • Abnormal serum FLC ratio (< 0.125 or > 8.0); serum FLC assay must be performed within 28 days of randomization • Measurable monoclonal protein in the serum (≥ 1.0 g/dL) or urine (≥ 200 mg/24 hrs) • No lytic lesions on skeletal surveys and no hypercalcemia (ie, ≥ 11 mg/dL)

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Cytogenetic abnormalities:

In terms of the risk of progression to MM, deletion 17p or t(4;14), gain of 1q21 and chromosomal trisomy have all been shown to be risk factors, with greater impact among those with a low disease burden at diagnosis. Survival after progression to active MM is similar to the established data in MM - poor OS for deletion 17p or t(4;14) anomalies but not for trisomy. In contrast, a recent GEP analysis indicates that SMM and MGUS share the same GEP abnormalities seen in active multiple myeloma (MM) but only the proliferation subtype was predictive of progression.

Time to revise the "CRAB" criteria:

Revision of current end organ damage criteria has been proposed by several groups including the IMWG. Some of the proposed criteria for re-classifying asymptomatic individuals as active MM pts needing therapy include: BM plasmacytosis ≥ 60%, involved free light chain >100 times the uninvolved or focal BM lesions detected by PET or MRI imaging. Newest NCCN criteria (version 2.2014) also recognize the need for reclassification of high risk SMM (Table 3).

PETHEMA – Qui REDEX Study and early treatment of SMM:

The established standard of care in SMM is close observation and treatment only after progression to active MM. This recommendation is based on the lack of survival or PFS benefit for agents such as melphalan, bisphosphonates or thalidomide in prior randomized trials. These findings have been recently challenged by the PETHEMA sponsored QUIREDEX study (NCT00480363) reported by Mateos et al. They randomized a strictly defined high risk sub group of SMM patients to Lenalidomide/low dose dexamethasone vs. observation. High risk was defined by 2 sets of inclusion criteria – one group included those with BM PC $\underline{\geq}$10% AND a high M spike which was set as ≥3 g/dl for IgG, ≥2 g/dl for IgA and $\underline{\geq}$1 g of urine M protein per 24 hours. Another group (40% of all pts) included those with only one of the above marrow or M spike criteria and $\underline{\geq}$ 95% phenotypically aberrant BM PCs detected by multi-parameter flow cytometry AND suppression of either of the uninvolved immunoglobulins (i.e IgA or M if IgG SMM) by at least 25%.

Those randomized to lenalidomide / low-dose dexamethasone arm had superior rates of freedom from progression to active MM (77% progression free at 3 yrs vs. 30%, p<0.001) and surprisingly a superior OS (94% alive at 3yrs vs. 80%, p=0.03) compared with the cohort randomized to observation.

This is the first randomized study to suggest survival advantage for early therapy in asymptomatic individuals with SMM albeit in a selected high risk subgroup. Several limitations of this study have been pointed out. Most importantly the sophisticated flow cytometry technique used limits the widespread use of these criteria in current practice. The unexpected observation of inferior survival among untreated SMM pts have led to speculation about the causes. Notably, those in the observation arm did not appear to receive uniform therapy with Lenalidomide based induction at clinical progression or initiation of therapy for asymptomatic biochemical progression which might explain why their 3 yr OS (80%) was not as impressive as current pts with newly diagnosed MM. The lack of genetic risk information and the older median age of the observation cohort could mean that baseline risks between cohorts could have been different. Once treatment is initiated should the high risk SMM pts just be considered active MM and receive standard induction, consolidation, autotransplant and maintenance approaches? The study actually raises more questions than answers.

Nevertheless, the principle that at least a subset of SMM pts benefit from early intervention is an important shift from the established paradigm. The subset of high risk pts stratified by M protein size and PC numbers alone has been estimated to be about 30% of the overall SMM group. Based on a Swedish population registry analysis, out of 360 pts diagnosed with SMM, 30% were defined as high risk by these criteria of whom 57% had progressed to active MM in 2 yrs and 70% by 30 months. The overall worldwide incidence of SMM of 0.44 cases per 100,000 persons means an incidence of high risk SMM in 0.14 cases per 100,000 persons. In terms of therapy costs, this could entail substantial costs to society.

Does my patient need treatment for SMM – rethinking the timing of therapy in SMM?

The exact intervention needed (e.g. reframe the diagnosis and treat as active MM vs. use a disease slowing drug) and an defining who needs therapy (flow cytometry, FISH abnormalities, disease burden markers, proteomics, genomics, advanced bone imaging) are all works in progress being tested in trials. Reclassification of disease staging is always fraught with the risk of "stage migration bias" which leads to spurious improvements in stage-specific prognosis. When previously lower risk patients are classified into the more severe disease stage on the basis of new early detection technology etc, an apparent improvement in survival can be seen in both groups. This limits the use of epidemiologic / registry data to analyze the benefit of early intervention for lower risk disease. National guidelines emphasize the importance of treating SMM pts as far as possible in prospective trials of intervention vs. no intervention.

A current US intergroup study (NCI E3A06, NCT01169337) randomizes pts with asymptomatic high risk SMM defined as BM PCs $\geq$10% or an abnormal FLC ratio to Lenalidomide vs. observation. Another current US trial (NCT01572480) explores the use of Carfilzomib/Lenalidomide/Dexamethasone induction in high risk pts defined by either the Mayo or PETHEMA criteria. It should be mentioned that neither lenalidomide or carfilzomib are approved by the US FDA for the treatment of smoldering myeloma and remain investigational at this time for this population of patients. Other agents are also undergoing investigation or are planned in this setting. While the benefits of early treatment and preventing early morbidity are clear for some pts, the potential risks include overtreatment of patients who may never need therapy or those who could have deferred therapy for years. Identification of risk and prediction of end organ damage are not exact at this time and prospective studies with longitudinal observation of larger cohorts of patients are needed.

Most recent NCCN consensus guidelines do NOT RECOMMEND treating all SMM pts, nor those considered at high risk based on PETHEMA study criteria. The consensus of the panel recommends observation at 3 to 6 mo intervals or enrollment in a clinical trial*. In an era of changing diagnostic criteria and uncertainty re: treatment initiation, referral to a specialized center for evaluation and trial / treatment recommendations is appropriate.*

Follow Up of Patient:

Mrs. NB has continued on follow up for the past 6 years with no further change in disease status. A follow up marrow was performed 1 year after diagnosis and multicolor flow cytometry identified aberrant plasma cells to be 100%. Most recent M spike and Igs are summarized below. Patient remains on clinical follow up with CBC, chemistry panels and biochemical myeloma markers every 6 months. Most recent M spike was 2.53 g/dl (see table 5).

Table 5. Immunoglobulin and free light chain component monitoring 2007 and 2013.

Component *Latest Ref Rng*	2007	2013
Immunoglobulin A Serum *70 - 400 mg/dL*	68	62 (L)
Immunoglobulin M Serum *40 - 230 mg/dL*	56	52
Immunoglobulin G Serum *700 - 1600 mg/dL*	3915	3304
Free Kappa *3.30 - 19.40 mg/L*	8.15	17.55
Free Lambda *5.71 - 26.30 mg/L*	57.46	102.86

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