Smoldering Multiple Myeloma

A Case Study

Case Presentation
53-Year-Old Male

- Patient presented for a routine exam
- No prior history of disease or family history of hematologic disorders or malignancies, was in relative good health
- Routine blood work was ordered which identified an elevated erythrocyte sedimentation rate with elevated serum proteins (90 g/L)

Identifying MGUS or SMM versus Active Multiple Myeloma

- Identifying a patient as either having MGUS, SMM or MM while excluding other possible diseases or causes depends on a differential diagnosis; there is no single test that will allow for the diagnosis of MGUS, SMM or MM

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

IMWG and NCCN Consensus

- The International Myeloma Working Group (IMWG) has issued consensus recommendations for the monitoring and treatment of SMM as has the National Comprehensive Cancer Network (NCCN)

NCCN Diagnostic Test Guidelines Initial Diagnostic Workup

- H&P
- CBC, differential, platelet count
- BUN/creatinine, electrolytes
- LDH
- Calcium/albumin
- Beta-2 microglobulin
- Serum free light chain assay
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24-hour urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Cytogenetics
- FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q211 amplification]

H&P=history and physical; CBC=complete blood count; BUN=blood urea nitrogen; LDH=lactate dehydrogenase; FISH=fluorescence *in situ* hybridization; MRI=magnetic resonance imaging

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Oncology: Multiple Myeloma, Version 2.2013 (release date: 03/08/2013).

NCCN Diagnostic Test Guidelines

- The following are considered useful under some circumstances
  - MRI
  - CT scan (avoid contrast)
  - PET/CT scan
  - Tissue biopsy to diagnose a osseous or extraosseous plasmacytoma
  - Bone densitometry
  - Plasma cell labeling index
  - Staining of marrow and fat pad for amyloid
  - Serum viscosity
  - HLA typing

MRI=magnetic resonance imaging; CT=computed tomography; PET=positron emission tomography; HLA=human leukocyte antigen

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Case Study: Laboratory Values

Lab/Normal Reference Range	Value
WBC 3.0–11.0 k/µL	5.67
Plt Ct 150–400 k/µL	320
Hgb 13.0–17.0 g/dL	13.5L
Hct 39.0–51.0%	44L
MCV 80–100 fL	90.8L
RDW-CV 11.5–15.0%	14.3
Neut % 38.5–75.0%	52.0
Abs Neut 1.00–7.50 k/µL	2.97

Lab/Normal Reference Range	Value
Creatinine 0.7–1.4 mg/dL	1.2
Albumin 3.5–5.0 g/dL	3.6L
β-2-microglobulin <0.27 mg/dL	

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

Case Study: Laboratory Values

SPEP: Lab/Normal Reference Range	Value
Alpha-1 0.11–0.22 g/dL	0.18
Alpha-2 Globulin 0.6–1 g/dL	0.72
Beta G 0.50–1.00 g/dL	0.68
Gamma Glob 0.60–1.35 g/dL	0.93
M-Spike (g/dL)	**3.8H**

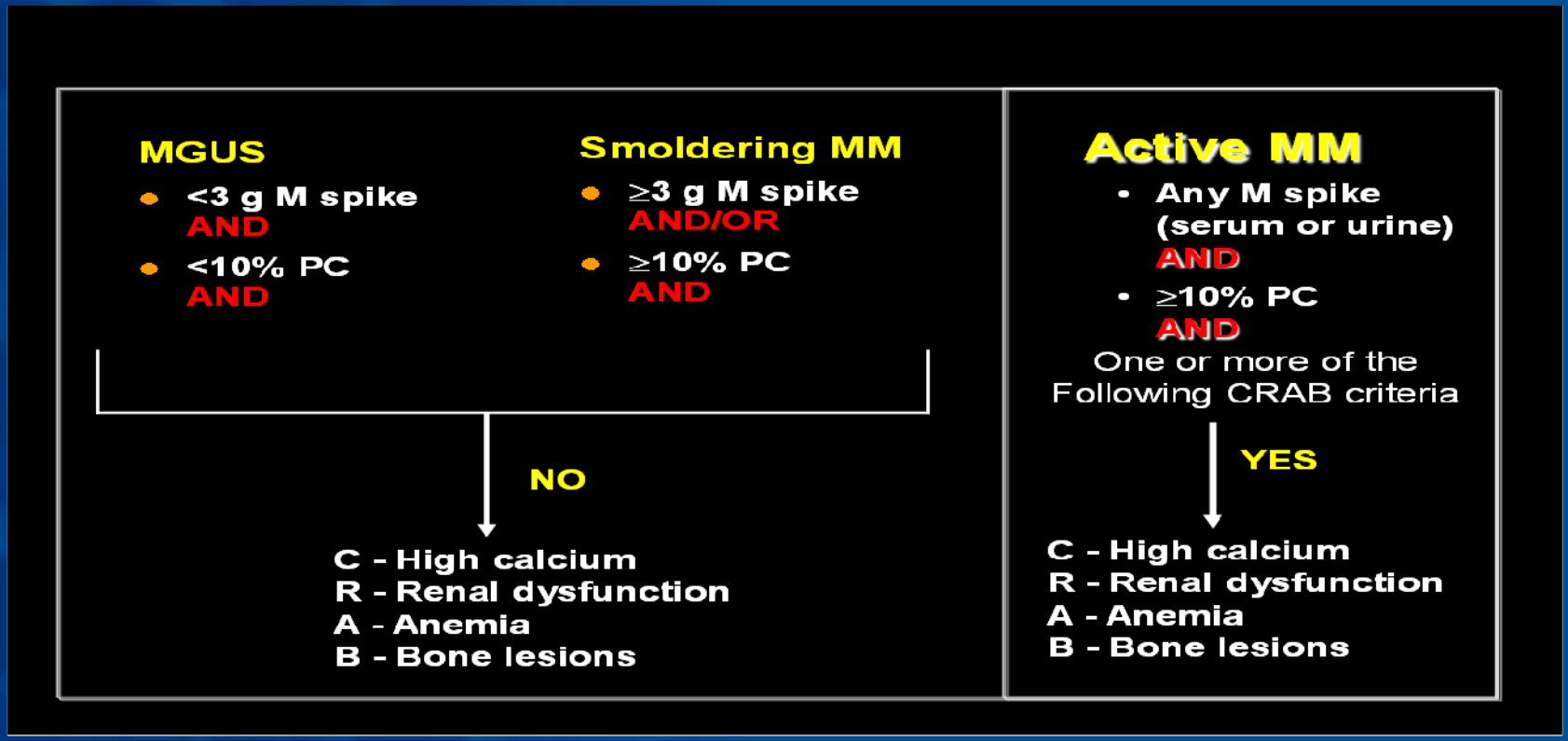
Lab/Normal Reference Range	Value
Serum IgG 717–1,411 mg/dL	2,100 (H)
Serum IgA 78–391 mg/dL	144
Serum IgM 53–334 mg/dL	189
Serum Kappa 534–1,267 mg/dL	**2,164 (H)**
Serum Lambda 253–653 mg/dL	266
sFLC K/L 0.26-1.65	**8.14 (H)**

Gamma Glob=gamma globulin; Ig=immunoglobulin; sFLC=serum free light chain;

Additional Laboratory Workup

- FISH revealed a 13q (retinoblastoma aka Rb) deletion as well as a translocation of 4;14 [t(4;14)]
- No lytic lesions were detected by radiographic skeletal survey including lateral radiograph of the skull, anteroposterior (AP) and lateral views of the spine, and AP views of the humeri, ribs, pelvis, and femora
- MRI showed osteoporosis but no lytic lesions were detected

NCCN Algorithm to Determine Active MM



Kyle RA, et al. *Leukemia.* 2009;23(1):3-9.; National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Oncology: Multiple Myeloma, Version 2.2013 (release date: 03/08/2013).; Kyle RA, et al. *Leukemia*. 2010;24(6):1121-1127.

IMWG Diagnostic Test Guidelines: Risk-stratification

- Risk factors significant for progression
  - Size of the serum monoclonal protein
  - Number of plasma cells in the bone marrow are the most important
  - The FLC (free light chain) ratio is an independent additional risk factor for progression
- Risk factors not significant for progression
  - Sex
  - Hemoglobin level
  - Type of serum heavy chain
  - Serum albumin value
  - Presence/type of urinary light chain
  - Reduction in levels of uninvolved immunoglobulins
  - Involvement of the inter fatty marrow space

Diagnosis Based on NCCN Guidelines

- Based on the presence of a ≥3 g/dL M-protein component (M-spike) as well as ≥10% clonal plasma cells observed in bone marrow biopsy but in the absence of end organ damage CRAB, this patient was diagnosed with asymptomatic or smoldering multiple myeloma (SMM)

CRAB=calcium, renal failure, anemia, or bone disease

Diagnosis Based on IMWG Guidelines

- Risk factors significant for progression
  - M-protein of ≥1.5 g/dL (3.8 g/dL)
  - PC of ≥10% (33%)
- Risk factors not significant for progression
  - IgG subtype
- However, the patient did have an abnormal FLC ratio (defined as ≤0.125 or ≥8), ≥8, which has predicted for higher rates of progression, hazard ratio, 2.3; 95% CI, 1.6–3.2)
- Based on the IMWG definition, this patient would be considered high-intermediate risk with the two identified risk factors. It may also be considered that the patient has an additional risk factor with the presence of t(4;14), whereas the patient's del(13q14) does not contribute to risk according to the Neben, et al., study from ASH 2012 (n=248)

PC=plasma cells; CI=confidence interval

Dispenzieri A, et al. *Blood*. 2008;111:785-789.; Neben, et al. ASH 2012 (Abstract 1806), poster presentation.

Treatment Plan

- The patient was given bisphosphonate (zoledronic acid) support for his osteoporosis and then was monitored in accordance with NCCN and IMWG guidelines at 3 months and again at 6 months at which time the patient was referred to an Eastern Cooperative Group Trial for intermediate-high risk SMM patients

Current Standard of Care and Follow-up Monitoring

- The NCCN guidelines (category 1) and the IMWG consensus recommendations include observation during defined intervals or clinical trial as the treatment plan for SMM patients
- The IMWG specifically states that patients such as this one, "with smoldering myeloma with FLC ratio ≤0.125 or ≥8 plus ≥10% plasma cells in the marrow are at high risk of progression in the first 2 years following recognition. These patients should be considered candidates for chemoprevention trials. However, off-study, observation is still the standard even in this group"
- According to the IMWG and NCCN serum protein electrophoresis, complete blood count, measurement of calcium and creatinine values and 24-hour urine collection for electrophoresis and immunofixation should be performed at diagnosis and in 2-3 months after the initial recognition of SMM (IMWG) or 3 to 6 month intervals (NCCN)

Kyle RA, et al. *Leukemia*.2010;24(6):1121-1127.

Current Standard of Care and Follow-up Monitoring

- A baseline bone marrow biopsy as well as a skeletal survey are mandatory
- MRI of the spine and pelvis is recommended (detect occult lesions, and when present, predict for a more rapid progression to symptomatic myeloma)
- If the results are stable, the studies should be repeated every 4-6 months for 1 year and, if stable, evaluation can be lengthened to every 6-12 months
- A skeletal survey should be performed if there is evidence of progression in routine studies

Current Clinical Trials
Spanish PATHEMA Group

- Randomized, open-label, phase III trial
- Early treatment of high-risk smoldering myeloma delays progression to active disease and increases overall survival (OS)
- 119 patients enrolled for treatment or observation
- Treatment group received induction regimen (len, 25 mg/day on days 1 to 21, plus dex, 20 mg/day on days 1 to 4 and 2 to 15, at 4-week intervals for nine cycles), followed by a maintenance regimen (len ,10 mg/day on days 1 to 21 of each 28-day cycle for 2 years)
- Primary endpoint was time to progression (TTP) to symptomatic disease. Secondary endpoints were response rate, OS, and safety
- 40 months, the median TTP was significantly longer in the treatment group than in the observation group (median not reached vs. 21 months; hazard ratio for progression, 0.18; 95% CI, 0.09 to 0.32; *P*<.001). The 3-year survival rate was also higher in the treatment group (94% vs. 80%; hazard ratio for death, 0.31; 95% CI, 0.10 to 0.91; *P*=.03)
- Partial response (PR) or better was achieved in 79% of patients in the treatment group after the induction phase and in 90% during the maintenance phase. Toxicity was mainly grade 2 or lower

Mateos MV, et al. *N Engl J Med.* 2013;369(5):438-447.

Current Clinical Trials ECOG-E3A06

- Randomized phase III trial, currently recruiting
- Patients with an M-protein and greater than 10% plasma cells but do not have CRAB and have clones of plasma cells in the bone marrow, and measurable blood or urine protein
- Enrolled patients will get single-agent lenalidomide or observation
- Asymptomatic high-risk smoldering myeloma patients may provide insight regarding the benefits and risks of treatment versus observation and not just in high-risk patients but also in intermediate-risk patients

ClinicalTrials.gov Identifier: NCT01169337