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PEARLS OF LABORATORY MEDICINE

Pearl Title: Diagnostic Criteria for Multiple Myeloma

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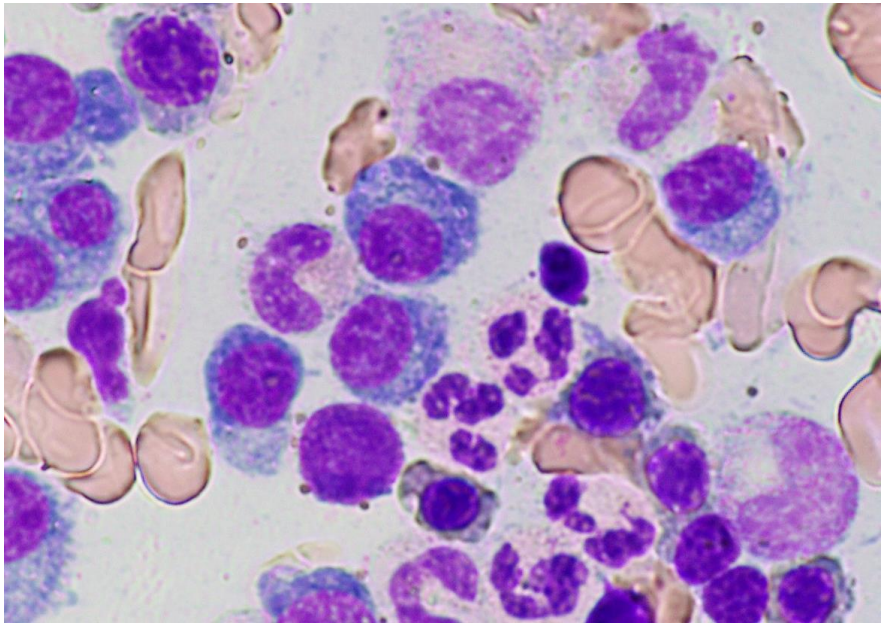
What is Multiple Myeloma?

- Hematological Cancer
- Develops in the bone marrow
- Cancer of PLASMA CELLS



Photomicrographs courtesy of Mikhail Roshal MD, Department of Pathology, MSKCC

Monoclonal Gammopathies

- Group of diseases characterized by expansion of a single clone of plasma cells
  - MGUS
  - Smoldering multiple myeloma
  - Waldenstrom's Macroglobulinemia
  - Solitary Plasmacytoma
  - AL amyloidosis
  - POEMS
  - Multiple Myeloma

Epidemiology of MM

- Incidence of 4-5/100,000
- 1% of all cancers
- 10% of hematologic malignancies in the US
- Median age at diagnosis: 66
- Risk factors
  - advanced age
  - black race
  - Males
  - family history

Clinical Aspects of Multiple Myeloma

- Pathophysiology
  - Hypercalcemia
    - due to bone lytic lesions
    - neurological symptoms
  - Renal insufficiency
    - tubular damage by free light chains
  - Anemia
    - overgrowth of plasma cells leads to crowding out of cells for RBC production
  - Bone lesions
    - fractures due to lytic lesions caused by plasma cell expansion in marrow

- Natural Course
  - Fatal without treatment
  - Incurable, but highly effective treatments available
  - Patients generally relapse after treatment
  - Patients can undergo multiple treatments
  - Need to constantly monitor disease to detect relapse

Tests Vital to Diagnosis/Monitoring of MM

- Clinical examination/history
- Imaging
  - X-ray
  - CT
  - MRI
  - PET scan
- Pathology
  - bone marrow aspirate/biopsy
- Laboratory Tests
  - hematologic
  - chemistry
    - calcium
    - creatinine
  - serum protein electrophoresis/immunofixation
  - urine protein electrophoresis/immunofixation
  - serum free light chains

International Myeloma Working Group (IMWG)

- Offshoot of International Myeloma Foundation
- International consortium of > 200 leading myeloma researchers
- Develop guidelines for diagnosis, management, response criteria, etc
- Constantly evolving and updated
- Last update for diagnostic criteria issued 2014

2014 IMWG criteria for the Diagnosis of MM

- Clonal bone marrow plasma cells ≥ 10% or biopsy proven bony or soft tissue plasmacytoma (clonality must be established by flow, IHC, or IF)

PLUS

- Presence of related organ or tissue impairment (CRAB)

OR

- Presence of a biomarker associated with near inevitable progression to end-organ damage

*Rajkumar et al. Lancet Oncol 2014;15:e538-48.

Presence of related organ or tissue impairment (CRAB)

- Anemia
  - hemoglobin < 10g/dL or
  - 2g/dL below normal
- Hypercalcemia
  - serum calcium > 11 mg/dL
- Renal insufficiency
  - eGFR/GFR < 40 ml/min OR
  - serum creatinine > 2mg/dL
- Bone lesions
  - one or more osteolytic lesions on skeletal radiography, MRI, CT or PET/CT

*Rajkumar et al. Lancet Oncol 2014;15:e538-48.

Presence of a biomarker associated with near inevitable progression to end-organ damage: Myeloma Defining Events (MDE's)

1. ≥ 60% clonal plasma cells in bone marrow

2. involved/uninvolved FLC ratio of 100 or more (involved FLC must be ≥ 100 mg/L)

3. MRI with more than one focal lesion (involving bone or bone marrow)

*Rajkumar et al. Lancet Oncol 2014;15:e538-48.

Other Monoclonal Gammopathies/Plasma Cell Disorders

- Smoldering Multiple Myeloma
- Monoclonal Gammopathy of Undetermined Significance (MGUS)
- Solitary Plasmacytoma
- POEMS Syndrome
- Light Chain Amyloidosis

International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma

Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-73. Epub 2006/07/21. doi: 10.1038/sj.leu.2404284. PubMed PMID: 16855634

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Response	*IMWG criteria*
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,[5] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA

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No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA
Progressive disease[5]	Increase of ≥ 25% from lowest response value in any one or more of the following: • Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[6] • Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) • Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%[7] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[6] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] • Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] • Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]
Relapse from CR[5] (To be used only if the end point studied is DFS)[8]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% plasma cells in the bone marrow[7] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

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2. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-48. Epub 2014/12/03. doi: 10.1016/S1470-2045(14)70442-5. PubMed PMID: 25439696.

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4. International Myeloma Working Group www.imwg.myeloma.org

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
- **Consultant or Advisory Role:** No disclosures
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- **Patents:** No disclosures

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