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laboratory medicine.*

PEARLS OF LABORATORY MEDICINE

Pearl Title: Diagnostic Criteria for Multiple Myeloma

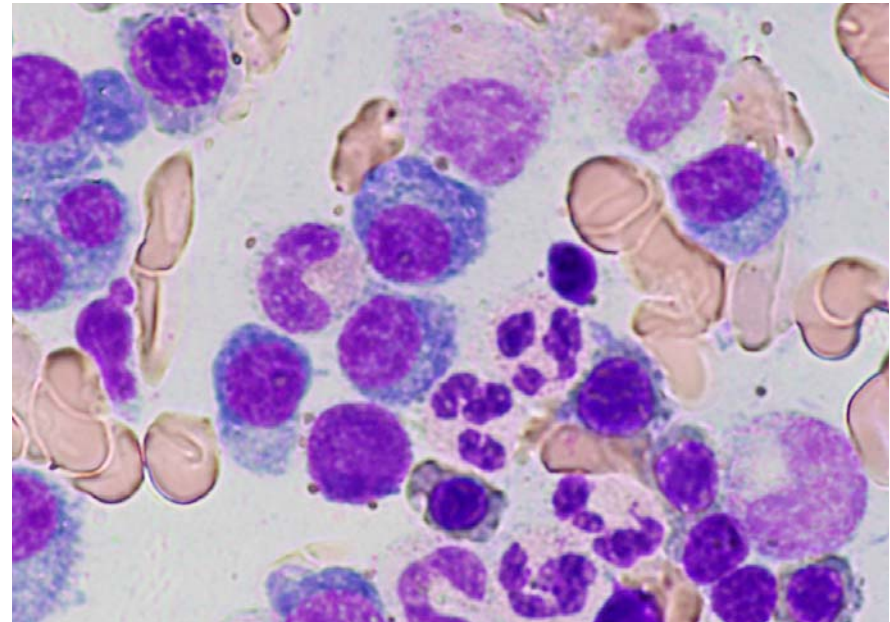
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What is Multiple Myeloma?

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



Photomicrographs courtesy of Mikhail Roshal MD,
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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 $\geq 10\%$ 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

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

1. $\geq 60\%$ 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)

Other Monoclonal Gammopathies/Plasma Cell Disorders

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

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

No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA
Progressive disease ⁵	<p>Increase of $\geq 25\%$ from lowest response value in any one or more of the following:</p> <ul style="list-style-type: none"> • 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/dL⁷ • Bone marrow plasma cell percentage; the absolute percentage must be $\geq 10\%$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	<p>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</p> <ul style="list-style-type: none"> • 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	<p>Any one or more of the following:</p> <ul style="list-style-type: none"> • Reappearance of serum or urine M-protein by immunofixation or electrophoresis⁷ • Development of $\geq 5\%$ plasma cells in the bone marrow⁷ • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

References

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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:**
- **Consultant or Advisory Role:**
- **Stock Ownership:**
- **Honoraria:**
- **Research Funding:**
- **Expert Testimony:**
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