**Plasma Cell Myeloma (PCM)**

Proliferation of neoplastic plasma cells in bone marrow with serum and/or urine M protein and evidence of organ damage

**Clinical:** A common hematologic neoplasm (15%), accounts for 20% death of all hematologic malignancies

Affects primarily elderly (90% cases in >50 years), median age ~70 years. Black:White 2:1

Arises from precursor lesion MGUS

Symptoms of end organ damage (CRAB): hypercalcemia, renal insufficiency, anemia, bone pain (lytic bone lesion). Other symptoms: infection, bleeding, neuropathy

**Blood morphology:** Red blood cell rouleaux formation in some patients. Plasma cells in blood uncommon

**Bone marrow:** Amount of plasma cells in bone marrow varies (10%-100%). Patterns of bone marrow involvement: nodular, interstitial, diffuse

**Morphologic types**

- **Common type:** Enlarged nuclei, often with a small nucleolus, increased pale cytoplasm
- **Plasmablastic type:** Higher N:C ratio with larger, round nuclei, prominent single nucleolus, variable blue cytoplasm
- **Small cell type:** Smaller cell size resembling lymphoplasmacytic cells, small round nuclei without nucleolus, scant eccentric cytoplasm

**Other morphologies:** Flame cells (red cytoplasm, usually IgA type), Dutcher body (pseudo-nuclear inclusion), Russell body (cytoplasmic inclusion)

**Phenotype:** CD38+, CD138+, CD56+ 75% (aberrant), CD117+ 25% (aberrant), LCA-, B-cell markers (CD19, CD20, CD22) negative, surface kappa and lambda negative, cytoplasmic kappa+ or lambda+ (monoclonal)

**Small cell type:** above phenotype plus Cyclin D1+, often CD20+

**Lab test:**

- **Serum protein electrophoresis:** Serum M protein in 97% cases: IgG ~50%, IgA ~20%, light chain ~20%, IgD, IgE and biclonal <10%. Non-secretory ~3%
- **Urine protein electrophoresis:** Urine M protein light chain only (Bence Jones protein), heavy chain present in advanced cases (more severe renal damage)
- **Serum quantitative immunoglobulins and free kappa to lambda ratio:** for disease monitor
- **Serum Beta2 microglobulin:** for clinical staging
- **Clonality of plasma cells in bone marrow:** in situ hybridization or flow cytometry

**Cytogenetics:**

- >90% cases have genetic changes detected by FISH
- Translocations involving IGH locus (14q32) with various partners in 55-70%, hyperdiploidy in 30-40%, 13q14 deletion in ~50%, TP53 (17p13) deletion, 1q gain, or 1p deletion in small numbers

**Prognosis and Therapy:**

Survival varies from < 6 months to >10 years (median ~5.5 years)

Unfavorable prognostic factors: >70 years, poor performance status, high stage disease, unfavorable genetic changes (TP53 deletion, MAF translocation), minimal residual disease after therapy
Considered incurable disease. Single or combination chemotherapy, targeted therapy (Daratumumab), autologous stem cell transplant

### Genetics and Prognosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploidy</td>
<td>45%</td>
<td>Standard</td>
</tr>
<tr>
<td>t(11;14) IGH/Cyclin D1</td>
<td>16%</td>
<td>Standard</td>
</tr>
<tr>
<td>Cyclin D1 amplification</td>
<td>10-15%</td>
<td>Standard</td>
</tr>
<tr>
<td>t(4;14) IGH/NSD2</td>
<td>15%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Deletion 13q14</td>
<td>~50%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>t(14;16) IGH/MAF</td>
<td>~8%</td>
<td>High</td>
</tr>
<tr>
<td>Deletion 17p (TP53)</td>
<td>~10%</td>
<td>High</td>
</tr>
<tr>
<td>t(14;20) IGH/MAFB</td>
<td>~2%</td>
<td>High</td>
</tr>
</tbody>
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Standard: 8-10 years OS; Intermediate: 4-5 years OS; High: 3 year OS

### Variants:

**Smoldering (asymptomatic) plasma cell myeloma**

10-60% plasma cells in bone marrow or M protein at myeloma level, without evidence of organ damage

- Invariably progresses to symptomatic myeloma (median 5 years)
- Plasma cell morphology, phenotype, genetics similar to PCM (with lower frequencies)
- Managed by “watch and wait”

**Plasmacytoma**

**Solitary plasmacytoma of bone**

- Solitary mass of monoclonal plasma cells in bone
- Accounts for 1-2% of plasma cell neoplasm, most commonly involves vertebra, ribs
- Bone marrow negative or low levels (<10%) of clonal plasma cells
- May progress to PCM (more likely to progress when evidence of clonal plasma cells in bone marrow is present)

- Managed by local excision/radiation or similarly to PCM
- Differential diagnosis: Plasmablastic lymphoma (HIV+, EBV+, CD56-)

**Extraosseous (extramedullary) plasmacytoma**

- Solid lesion of monoclonal plasma cells in tissues other than bone
- Can occur in any organ/tissue (most common upper respiratory tract)
- Plasma cell morphology, phenotype, genetics similar to PCM
- 15% progress to PCM

- Managed by location radiation therapy
- Differential diagnosis: Plasmablastic lymphoma (HIV+, EBV+, CD56-)

**Plasma cell leukemia (PCL)**

- Clonal plasma cells in blood with >20% WBC or >2 x 10^9/L
- 2-4% plasma cell neoplasm present as PCL, 1% PCM transform to PCL
- CD20+ more frequent, CD56+ less frequent compared to PCM
- Extensive bone marrow involvement
- Aggressive course, poor response to therapy, shorter survival

**Plasma cell myeloma with associated syndrome**

**POEMS Syndrome:** polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes
TEMPI Syndrome: telangiectasia, erythrocytosis, monoclonal gammopathy, perinephric fluid, intrapulmonary shunting

Diagnostic criteria of plasma cell myeloma

<table>
<thead>
<tr>
<th><strong>Plasma cell myeloma</strong></th>
<th><strong>Smoldering myeloma</strong></th>
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</thead>
<tbody>
<tr>
<td>Clonal plasma cells &gt;10% in bone</td>
<td>Clonal plasma cells &gt;10% in bone marrow or serum</td>
</tr>
<tr>
<td>marrow or plasmacytoma, and</td>
<td>M protein &gt;3 g/dL or urine M protein &gt;500 mg,</td>
</tr>
<tr>
<td>Evidence of organ damage (any of</td>
<td>and</td>
</tr>
<tr>
<td>the following: hypercalcemia,</td>
<td>Absence of myeloma-defining organ damage or</td>
</tr>
<tr>
<td>renal insufficiency, anemia,</td>
<td>amyloidosis</td>
</tr>
<tr>
<td>bone lesion), or</td>
<td></td>
</tr>
<tr>
<td>Clonal plasma cells &gt;60% in bone</td>
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<tr>
<td>marrow, or</td>
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<tr>
<td>&gt;1 local lesions of plasmacytoma</td>
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</tbody>
</table>

**Plasma cell leukemia**

Clonal plasma cells in blood >20% WBC or >2 x 10⁹/L

**Plasmacytoma**

Solitary clonal plasma cell tumor(s) in bone or soft tissue

Monoclonal Gammapathy of Undetermined Significance (MGUS)

A precursor lesion of plasma cell myeloma with <10% clonal plasma cells in bone marrow and no myeloma-defining organ damage

Excludes IgM MGUS

**Clinical:** Serum M protein is usually found as an incidental finding (60% IgG, 15% IgA, 1% IgD, 1% IgE, 3% biclonal, 20% light chain only)

Affects primarily elderly (incidence of 3-5% in >50 years), uncommon in younger population

Black:White 2:1

No symptoms and signs

**Blood morphology:** No specific morphologic abnormalities

**Bone marrow:** Monoclonal plasma cells <10% in bone marrow

**Phenotype:** Similar to plasma cell myeloma, but less commonly CD56+ and CD117+

**Lab test:**

- *Serum protein electrophoresis:* Serum M protein <3 g/dL
- *Urine protein electrophoresis:* Urine M protein light chain <500 mg/24 hours
- *Clonality of plasma cells in bone marrow:* in situ hybridization or flow cytometry

**Cytogenetics:**

Genetic abnormalities are similar to myeloma, but in lesser frequency (~50%)

**Disease course:**

Most cases are stable

Risk of progression to myeloma or amyloidosis 0.3% to 12% per year (median 1%)

Increased risk of progression to myeloma: higher M protein level, higher bone marrow plasma cell level, IgA paraprotein, abnormal serum free light chain ratio, CD56+, unfavorable genomic abnormalities

Systemic amyloidosis

Tissue accumulation of intact or fragments of abnormal immunoglobulin light chain that forms beta-pleated sheets and causes organ dysfunction

**Clinical:** Incidence of new cases 0.01% per year, affects middle aged and elderly population
80% patients have associated MGUS, 20% patients have myeloma
Male:female: 2:1
Clinical presentation: peripheral neuropathy, carpal tunnel syndrome, bone pain, congestive heart failure, nephrotic syndrome, malabsorption, hepatomegaly, macroglossia, purpura, edema, fibrinolysis and DIC (factor X amyloid binding)
**Blood morphology:** No specific morphologic abnormalities
**Bone marrow:** Monoclonal plasma cells <10% in 80% cases, >10% in 20% cases
**Lab test:**
*Serum protein electrophoresis:* Serum M protein 1.4 g/dL in average
*Urine protein electrophoresis:* Urine M protein light chain often detectable
*Amyloid detection:* bone marrow biopsy, fat pad biopsy, kidney biopsy (bone marrow: amyloid often deposits in vessel wall and periosteum)
*Congo red stain:* Pink to red by light microscopy, “apple green” birefringence under polarize
**Differential diagnosis:**
Secondary or familial amyloidosis (AA amyloidosis, ATTR amyloidosis): Differentiated by mass spectrometry
**Prognosis:**
Survival varies from >10 years to 6 months
Unfavorable risk factors: cardiac involvement (most important), multiple organ involvement, >10% bone marrow plasma cells, high serum free light chain, high beta-2 microglobulin, high serum uric acid

**Light chain and heavy chain deposition disease**
Deposition of abnormal immunoglobulin light chain and/or heavy chain in tissue caused by plasma cell myeloma (most common) and other lymphoplasmacytic neoplasms
Unlike amyloidosis, the deposition does not form beta-pleated sheets, does not bind to congo red, does not contain amyloid P component
Kappa more common than lambda; light chain more common than heavy chain
**Clinical:** Median age 58 years, more common in men
Symptoms of organ dysfunction; renal symptoms most common
Other organs include liver, heart, peripheral nerve, blood vessel, bone marrow
**Blood morphology:** No specific morphologic abnormalities
**Bone marrow:** Amorphous eosinophilic material deposition; non-fibrillary; negative Congo red stain
Monoclonal plasma cells frequent in bone marrow
**Phenotype:** Phenotype similar to plasma cell neoplasm
**Lab test:** Serum M protein: 85% cases
**Cytogenetics:**
Genetic abnormalities are similar to myeloma
**Disease course:**
Median survival 4 - 14 years