Plasma Cell Neoplasms
Review and Case Studies

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Learning Objectives
1. Define monoclonal gammopathy
2. Compare and contrast the clinical and laboratory features of the following plasma cell disorders:
   - Plasmacytoma, Asymptomatic and Symptomatic plasma cell myeloma
   - Monoclonal gammopathy of undetermined significance (MGUS).
3. Differentiate lymphoplasmacytic lymphoma from plasma cell myeloma

Introduction
• Plasma Cell Myeloma (PCM) (multiple myeloma, myelomatosis, medullary plasmacytosis)
• B-cell neoplasm resulting from expansion of a single clone of plasma cells (PCs)
• Abnormal PCs synthesize monoclonal immunoglobulin (M protein), a monoclonal light chain (Bence Jones protein) or both.

Normal Plasma Cell

• Normal Plasma Cells
  - About 1% of the normal marrow cells
  - Ovoid cells with an ovoid nucleus set at 90° to cell orientation
  - Blue cytoplasm due to increase in ribosomal RNA in the RER making protein - immunoglobulin
Introduction

Protein factories producing immunoglobulin composed of Light chains (kappa and lambda) and Heavy chains (G, A, M, D or E)

Introduction

- PCM is clinically heterogeneous – from no symptoms to aggressive disease
- Usually confined to BM with extramedullary involvement only in end stage disease
- Represent 10-15% of all hematologic malignancies and 1% of all malignancies
- Median age at diagnosis is 70
- Males:Female 1.4:1 Twice frequency in African Americans as Caucasian Americans

World Health Organization Classification of Plasma Cell Neoplasms

- Monoclonal gammopathy of unknown significance
- Plasma cell myeloma
- Variants
  - Asymptomatic myeloma
  - Nonsecretory myeloma
  - Plasma cell leukemia
- Plasmacytoma
- Solitary osseous plasmacytoma
- Extramedullary plasmacytoma
- Immunoglobulin deposition diseases
- Primary amyloidosis
- Systemic light and heavy chain deposition diseases
- Osteosclerotic myeloma (POEMS [polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes] syndrome)

Monoclonal gammopathy of unknown significance

- Serum M protein present, <30 g/dL
- Bone marrow
  - Clonal plasma cells comprising <10% of nucleated cells in aspirate
  - Intramedullary infiltration present in biopsy sample
- No lytic bone lesions
- No myeloma-related end-organ injury or impairment
- No evidence of other B-cell lymphoproliferative disorder

Plasma cell myeloma

- Symptomatic
  - Serum or urine M protein present
  - Presence of clonal plasma cells in bone marrow or plasmacytoma
  - Myeloma-related end-organ injury or impairment
- Asymptomatic
  - Serum M protein present, >30 g/dL
  - Presence of clonal plasma cells in bone marrow, >10% of nucleated cells
  - No myeloma-related end-organ injury or impairment
  - Plasma cell leukemia
  - Presence of clonal plasma cells in peripheral blood, >2.0 x 10^9/L or >20% of WBCs

Clinical and Laboratory Features of Plasma Cell Myeloma

- 3 Diagnostic Criteria for Symptomatic PCM
  - M protein in serum or urine
  - Increased clonal bone marrow PCs
  - Presence of end-organ damage - CRAB
    - Hypercalcemia
    - Renal insufficiency
    - Anemia
    - Bone lesions
- Asymptomatic PCM – above criteria without CRAB
Clinical and Laboratory Features of Plasma Cell Myeloma

<table>
<thead>
<tr>
<th>Laboratory Features</th>
<th>Percentage of Patients</th>
</tr>
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<tbody>
<tr>
<td>Anemia (Hgb &lt; 12 g/dL)</td>
<td>71</td>
</tr>
<tr>
<td>Bone lesions (lytic, pathologic fractures, osteopenia)</td>
<td>80</td>
</tr>
<tr>
<td>Renal Failure (serum creatinine &gt;2.0 mg/dL)</td>
<td>19</td>
</tr>
<tr>
<td>Hypercalcemia (&gt; 11 mg/dL)</td>
<td>13</td>
</tr>
<tr>
<td>Monoclonal protein on serum protein electrophoresis</td>
<td>82</td>
</tr>
<tr>
<td>Monoclonal protein on serum protein immunofixation</td>
<td>93</td>
</tr>
<tr>
<td>Monoclonal protein on serum plus urine light chain</td>
<td>97</td>
</tr>
<tr>
<td>Immunofixation</td>
<td></td>
</tr>
<tr>
<td>Increased &gt;10% clonal plasma cells in bone marrow</td>
<td>96</td>
</tr>
<tr>
<td>Type of immunoglobulin</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>52</td>
</tr>
<tr>
<td>IgA</td>
<td>21</td>
</tr>
<tr>
<td>Light chain only</td>
<td>16</td>
</tr>
</tbody>
</table>

Morphology

- **Peripheral blood**
  - Clonal PCs rarely seen in PB except in Plasma cell leukemia (PCL)
  - Rouleaux of RBCs is common
    - Due to decreased net negative charge
    - Caused by the paraproteins (abnormal Ig)
  - Blue staining of background also due to paraproteins

**Rouleaux in PCM**

**Rouleaux vs Agglutination**

- In Bone Marrow plasma cells in PCM may be in Focal nodules, Interstitial clusters and Diffuse sheets

a – mature pattern  b – atypical nuclei
Clinical and Laboratory Features of Plasma Cell Myeloma

- As the disease progresses the diffuse pattern predominates.
- Normal hematopoiesis will be compromised.
- Increased osteoclastic activity results in lytic lesions of the flat bones.
- Hypercalcemia then occurs frequently.
- Immunochemical stains for CD138 may be used to quantitate the plasma cells.
- Stains for kappa and lambda light chains show clonality of the plasma cells.

Increased osteoclastic activity results in lytic lesions of the flat bones.

CD138 and light chain immunochemistry.

Flow Histogram showing weak CD45, bright positive for CD38 and CD138 and cytoplasmic kappa positivity.
Abnormal Plasma Cell Morphology

- Immunoglobulin Storage
  - Russell Bodies (Mott cells, morulae cells)
  - Dutcher Bodies
- Flame Cells
- Abnormal Granules
- Hemophagocytosis

<table>
<thead>
<tr>
<th>Frequency of Antigen Expression in Plasma Cell Myeloma*</th>
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<tbody>
<tr>
<td>Marker</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>CD138</td>
</tr>
<tr>
<td>CD20 (bright)</td>
</tr>
<tr>
<td>CD56</td>
</tr>
<tr>
<td>CD117</td>
</tr>
<tr>
<td>CD20</td>
</tr>
<tr>
<td>CD45 (bright)</td>
</tr>
<tr>
<td>CD19</td>
</tr>
<tr>
<td>MUM1</td>
</tr>
<tr>
<td>CD79a</td>
</tr>
<tr>
<td>PAX5</td>
</tr>
<tr>
<td>EBV</td>
</tr>
<tr>
<td>Cyclin D1</td>
</tr>
</tbody>
</table>
Dutcher Bodies

Extracellular Crystals - Ig

Flame Cells

Granules in PCs
Auer-like bodies in PCs
Hemophagocytosis by Myeloma Cells

Case 1

- 56-year-old man was hospitalized for altered mental status and was found to have right upper lobe pneumonia and acute renal failure.
- Lab studies revealed severe hypercalcemia at the level of 19 mEq/L, increased creatinine and anemia.
- Radiological findings were significant for extensive diffuse myelomatous lytic lesions in calvarium, pelvic bones and spine including a large destructive lesion of the L2 vertebral body.
- A bone marrow aspiration yielded 65% of plasma cells showing profound cellular and nuclear polymorphism.
A bone marrow aspiration yielded 65% of plasma cells showing profound cellular and nuclear polymorphism with mitotic figures.

Case 1

- An immunohistochemical stain for CD138, and in situ hybridization studies for kappa and lambda light chains performed on core bone marrow biopsy revealed kappa – restricted plasma cells in large aggregates.
- FISH analysis detected del(17p13.1), t(4;14)(p16.3;q32) and monosomy 13.

Case 1

- Flow cytometric analysis of DNA and cytoplasmic immunoglobulin (cIg) revealed discretely hypodiploid and hypotetraploid DNA content with lambda light chain excess in 44%.
- Immunophenotypic analysis revealed plasma cell population expressing CD45 (dim), CD138, and CD56.

Serum Protein Electrophoresis

<table>
<thead>
<tr>
<th>Protein</th>
<th>Fraction</th>
<th>%</th>
<th>Ref. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>28.7</td>
<td>54.5 - 65.9</td>
<td></td>
</tr>
<tr>
<td>Alpha 1</td>
<td>2.3</td>
<td>1.9 - 3.5</td>
<td></td>
</tr>
<tr>
<td>Alpha 2</td>
<td>7.3</td>
<td>8.9 - 14.2</td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>5.6</td>
<td>7.8 - 15.2</td>
<td></td>
</tr>
<tr>
<td>Gamma</td>
<td>50.2</td>
<td>9.8 - 17.9</td>
<td></td>
</tr>
</tbody>
</table>

Interpretation: Decreased albumin. A restriction band is present (M-protein) in the gamma globulin region.

Serum Protein Immunofixation

Demonstrates a monoclonal IgG kappa restricted kappa light chain.
Case 1

- Treatment
  - 10 days of radiation to the spine
  - Dexamethasone and other chemotherapy
  - Prepared for autologous bone marrow transplant
  - PCM remains incurable and patients eventually relapse and become refractory to treatment
  - Current treatment results in median survival of 5-7 years

Case 2

- 68 yr old male with liver disease and diabetes mellitus had a chemistry profile
  - Total Protein: 6.8 g/dL (6.0-8.5)
  - Albumin: 3.5 g/dL (3.3-5.2)
  - Globulin: 4.3 g/dL (2.3-3.5)
  - Calcium: normal
- SPE and Immunofixation: increased IgG with normal kappa and lambda values
- BM: No evidence of increased plasma cells (<1%)
- Skeletal survey: Negative

Case 2

- Monoclonal Gammopathy of Undetermined Significance – MGUS
  - No treatment needed, but monitoring every year for increases in serum protein and metabolic panel for renal function
  - 1%/year MGUS converts to PCM
  - MGUS is not considered neoplastic until M-protein is >3 g/dL and monoclonal PCS >10%

Case 3

- 59 yr old female with presenting symptoms of anemia
  - WBC count: 18.0 x 10^9/L
    - Differential showed 32% plasma cells
    - Absolute plasma cell count: 5.7 x 10^9/L
  - SPE and Immunofixation: IgG monoclonal protein with kappa light chains in plasma and urine (Bence-Jones protein)
- Diagnosed as Plasma Cell Leukemia
- Criteria:
  - >20% clonal plasma cells in PB or >2.0 x 10^9/L PCs
  - Primary or Secondary to PCM
  - Secondary usually terminal phase of PCM
- Most PCL are CD56 negative
  - CD56 adhesion protein usually anchors plasma cells in the marrow
Case 4

- 59 year old with anemia as an incidental finding. Rouleaux was noted on the peripheral smear as well as increased small lymphs, plasmacytoid lymphocytes and plasma cells.
- Chemistry results:
  - Total Protein: 10.6 g/dL
    - IgA and IgG - Normal
    - IgM - 5.1 g/dL
  - SPE and Immunofixation showed IgM with lambda light chains
  - Serum viscosity – 2x normal

Plasmacytoid Lymphocytes

- Flow cytometry:
  - CD 19 and CD 20 positive clone
  - Also positive for CD23 and negative for CD5 and CD10
- Cytogenetics:
  - 6q- and a deletion of long arm of chromosome 16
  - Radiographic studies were negative

Bone Marrow aspirate

IgM filled vacuoles
**Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia**

- Waldenstrom macroglobulinemia (WM) is a rare and currently incurable neoplasm of IgM-expressing B-lymphocytes
- Characterized by the occurrence of a monoclonal IgM paraprotein in blood serum
- Infiltration of the hematopoietic bone marrow with malignant lymphoplasmacytic cells.

**WM** is associated (subset) with most cases of Lymphoplasmacytic Lymphoma (LPL).
- LPL occasionally IgA or IgG is the immunoglobulin, but when IgM, it is usually WM.
- Rare disease of older adults
- Deposition of IgM in tissues results in organ symptoms

**PCM and ??? - 1**

A 93-year-old man presented with lower extremity pain, and during evaluation for possible deep vein thrombosis, he was found to be pancytopenic.

**PCM and ??? - 2**

Chance identification of synchronous HCL and plasma cell myeloma in a potential HSC donor.

**PCM and ??? - 3**

Plasma Cell myeloma and acute myeloid leukemia

**References**