Diagnosis and differential diagnosis of multiple myelomas

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells within the bone marrow, leading to the overproduction of monoclonal immunoglobulins (M-proteins). This disease can result in various clinical manifestations, including bone lesions, anemia, renal dysfunction, and immunodeficiency.

Clinical Presentation

Patients with MM may present with a range of symptoms and laboratory abnormalities:

- **Bone Pain**: Often due to osteolytic lesions, commonly affecting the spine and ribs.
- **Hypercalcemia**: Resulting from bone resorption, leading to symptoms like nausea, vomiting, constipation, and confusion.
- **Renal Impairment**: Caused by light chain deposition, hypercalcemia, or hyperuricemia.
- **Anemia**: Due to marrow infiltration by malignant plasma cells and decreased erythropoiesis.
- **Infections**: Increased susceptibility due to impaired normal immunoglobulin production.

Diagnostic Criteria

According to the International Myeloma Working Group (IMWG), the diagnosis of MM requires:

1. **Clonal Bone Marrow Plasma Cells**: ?10% or biopsy-proven plasmacytoma.
2. **Myeloma-Defining Events (MDEs)**: At least one of the following:

- **CRAB Features**:
  - **C**alcium elevation: Serum calcium >11 mg/dL (>2.75 mmol/L).
  - **R**enal insufficiency: Serum creatinine >2 mg/dL or creatinine clearance <40 mL/min.
  - **A**nemia: Hemoglobin <10 g/dL or >2 g/dL below the normal limit.
  - **B**one lesions: One or more osteolytic lesions on imaging.
- **Biomarkers**:
  - Clonal bone marrow plasma cells ?60%.
  - Involved/uninvolved serum free light chain ratio ?100, with involved light chain ?100 mg/L.
  - More than one focal lesion ?5 mm on MRI.

Laboratory and Imaging Studies

- **Complete Blood Count (CBC)**: To assess for anemia and leukopenia.
- **Serum Chemistry Panel**: Including calcium, creatinine, and albumin levels.
- **Serum and Urine Protein Electrophoresis (SPEP and UPEP)**: To detect M-proteins.
- **Immunofixation Electrophoresis**: To identify the type of monoclonal protein.
- **Serum Free Light Chain Assay**: To quantify kappa and lambda light chains.
- **Bone Marrow Biopsy**: To determine the percentage of plasma cell infiltration.

- **Imaging**:
  - **Skeletal Survey**: To identify lytic bone lesions.
  - **MRI or PET-CT**: For detailed assessment of bone marrow involvement and extramedullary disease.

Staging Systems

Durie-Salmon Staging System

An older system based on clinical and laboratory parameters:

- **Stage I**: Low M-protein levels, normal calcium, hemoglobin >10 g/dL, normal bone structure.
- **Stage II**: Intermediate findings.
- **Stage III**: High M-protein levels, hypercalcemia, hemoglobin <8.5 g/dL, advanced lytic bone lesions.

International Staging System (ISS)

A more recent system utilizing

- **Stage I**: Serum ?2-microglobulin <3.5 mg/L and serum albumin ?3.5 g/dL.
- **Stage II**: Neither Stage I nor Stage III criteria met.
- **Stage III**: Serum ?2-microglobulin ?5.5 mg/L.

Differential Diagnosis

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- **Serum M-protein**: <3 g/dL.
- **Bone Marrow Plasma Cells**: <10%.
- **No CRAB Features**: Absence of end-organ damage.

Smoldering Multiple Myeloma (SMM)

- **Serum M-protein**: ?3 g/dL and/or bone marrow plasma cells 10–60%.
- **No CRAB Features**: Asymptomatic with no end-organ damage.

Primary Amyloidosis (AL)

- **Organ Involvement**: Cardiac, renal, hepatic, or peripheral nervous system.
- **Laboratory Findings**: Presence of monoclonal light chains; confirmed by tissue biopsy with Congo red staining.

Metastatic Carcinoma

- **Bone Lesions**: Can mimic MM lytic lesions.
- **Differentiation**: Requires imaging, biopsy, and immunohistochemical staining to identify

primary tumor origin.

Plasma Cell Leukemia (PCL)

A rare and aggressive variant of MM characterized by:

- **Peripheral Blood Plasma Cells**:
  - 2 × 10^9/L or >20% of leukocytes.
- **Clinical Features**: More aggressive disease with extramedullary involvement, anemia, thrombocytopenia, and renal dysfunction.
- **Treatment**: Requires prompt initiation of combination chemotherapy, often including proteasome inhibitors (e.g., bortezomib) and immunomodulatory agents (e.g., lenalidomide), followed by consideration of autologous stem cell transplantation