MULTIPLE MYELOMA

Dr. Usman
FCPS (Hematology)
Assistant Professor
Department of Pathology
Independent Medical College
Faisalabad

Correspondence Address:
Dr. Usman
FCPS (Hematology)
Assistant Professor
Department of Pathology
Independent Medical College, Faisalabad

Article received on: 11/04/2016
Accepted for Publication: 18/05/2016
Received after proof reading: 30/06/2016

Article Citation: Usman, Multiple Myeloma. Indep Rev Apr-Sep 2016;18(4-9): 158-162.

Key Concepts
- Pathophysiology of Multipe Myeloma
- Diagnosis of Multipe Myeloma
- Management of Multipe Myeloma
- Conditions for chemotherapy in Multiple Myeloma

Abstract: Multiple myeloma (MM) is a debilitating malignancy that is part of a spectrum of diseases. MM is characterized by neoplastic proliferation of plasma cells involving more than 10% of the bone marrow. The pathophysiologic basis for the clinical sequelae of MM involves the skeletal, hematologic, renal, and nervous systems. The presentation of MM can range from asymptomatic to severely symptomatic, with complications requiring emergent treatment. MM is often discovered through routine blood screening when patients are being evaluated for unrelated problems. Serum and urine assessment for monoclonal protein. There is currently no cure for MM. However, advances in therapy, such as autologous stem cell transplantation, radiation, and surgical care in certain cases, have helped to lessen the occurrence and severity of adverse effects of this disease and to manage associated complications.

Keywords: Multiple Myeloma, Bence jones Proteins, Bortezomib, Melphalan

Definition
Multiple myeloma (MM) is a debilitating malignancy that is part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia. First described in 1848, MM is characterized by a proliferation of malignant plasma cells and a subsequent overabundance of monoclonal paraprotein.

Pathophysiology
MM is characterized by neoplastic proliferation of plasma cells involving more than 10% of the bone marrow (see the images below). Increasing evidence suggests that the bone marrow microenvironment of tumor cells plays a pivotal role in the pathogenesis of myelomas.[13] This information has resulted in the expansion of treatment options.

The malignant cells of MM, plasma cells, and plasmacytoid lymphocytes are the most mature cells of B-lymphocytes. B-cell maturation is associated with a programmed rearrangement of DNA sequences in the process of encoding the structure of mature immunoglobulins. It is characterized by overproduction of monoclonal immunoglobulin G (IgG), immunoglobulin A (IgA), and/or light chains, which may be identified with serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP).
The role of cytokines in the pathogenesis of MM is an important area of research. Interleukin (IL)-6 is also an important factor promoting the in vitro growth of myeloma cells. Other cytokines are tumor necrosis factor and IL-1β.

The pathophysiologic basis for the clinical sequelae of MM involves the skeletal, hematologic, renal, and nervous systems, as well as general processes (see below).

**Skeletal processes**
Plasma-cell proliferation causes extensive skeletal destruction with osteolytic lesions, anemia, and hypercalcemia. Mechanisms for hypercalcemia include bony involvement and, possibly, humoral mechanisms. Isolated plasmacytomas (which affect 2-10% of patients) lead to hypercalcemia through production of the osteoclast-activating factor. Destruction of bone and its replacement by tumor may lead to pain, spinal cord compression, and pathologic fracture. The mechanism of spinal cord compression symptoms may be the development of an epidural mass with compression, a compression fracture of a vertebral body destroyed by multiple myeloma, or, rarely, an extradural mass. With pathologic fracture, bony involvement is typically lytic in nature.

**Hematologic processes**
Bone marrow infiltration by plasma cells results in neutropenia, anemia, and thrombocytopenia. In terms of bleeding, M components may interact specifically with clotting factors, leading to defective aggregation.

**Renal processes**
The most common mechanisms of renal injury in MM are direct tubular injury, amyloidosis, or involvement by plasmacytoma.[14, 15] Renal conditions that may be observed include hypercalcemic nephropathy, hyperuricemia due to renal infiltration of plasma cells resulting in myeloma, light-chain nephropathy, amyloidosis, and glomerulosclerosis.

**Neurologic processes**
The nervous system may be involved as a result of radiculopathy and/or cord compression due to nerve compression and skeletal destruction (amyloid infiltration of nerves).

**General processes**
General pathophysiologic processes include hyperviscosity syndrome. This syndrome is infrequent in MM and occurs with IgG1, IgG3, or IgA. MM may involve sludging in the capillaries, which results in purpura, retinal hemorrhage, papilledema, coronary ischemia, or central nervous system (CNS) symptoms (eg, confusion, vertigo, seizure). Cryoglobulinemia causes Raynaud phenomenon, thrombosis, and gangrene in the extremities.

**Etiology**
The cause of multiple myeloma has not yet been identified. Although scientists have made advancements in understanding how multiple myeloma develops, it is unclear as to what exactly causes the disease.

**Multiple Myeloma Risk factors**
Research suggests possible associations with a decline in the immune system, certain occupations, exposure to certain chemicals, and exposure to radiation. However, there are no strong connections, and, in most cases, multiple myeloma develops in individuals who have no known risk factors. Multiple myeloma may also be the result of several risk factors acting together.

While multiple myeloma is not considered to
be a hereditary disease, research has found that genetic factors may influence the development of multiple myeloma.

**Signs and symptoms**
The presentation of MM can range from asymptomatic to severely symptomatic, with complications requiring emergent treatment. Systemic ailments include bleeding, infection, and renal failure; pathologic fractures and spinal cord compression may occur.

Presenting symptoms of MM include the following:
- Bone pain
- Pathologic fractures
- Weakness, malaise
- Bleeding, anemia
- Infection (often pneumococcal)
- Hypercalcemia
- Spinal cord compression
- Renal failure
- Neuropathies

**Diagnosis and Investigations**
MM is often discovered through routine blood screening when patients are being evaluated for unrelated problems. In one third of patients, the condition is diagnosed after a pathologic fracture occurs, usually involving the axial skeleton.

Examination for MM may reveal the following:

**HEENT examination:** Exudative macular detachment, retinal hemorrhage, or cotton-wool spots

**Dermatologic evaluation:** Pallor from anemia, ecchymoses or purpura from thrombocytopenia; extramedullary plasmacytomas (most commonly in aerodigestive tract but also orbital, ear canal, cutaneous, gastric, rectal, prostatic, retroperitoneal areas)

Musculoskeletal examination:
Bony tenderness or pain without tenderness

Neurologic assessment: Sensory level change (ie, loss of sensation below a dermatome corresponding to a spinal cord compression), neuropathy, myopathy, positive Tinel sign, or positive Phalen sign

**Abdominal examination:**

**Hepatosplenomegaly**
Cardiovascular evaluation: Cardiomegaly

In patients with MM and amyloidosis, the characteristic examination findings include the following:
- Shoulder pad sign
- Macroglossia
- Typical skin lesions
- Postprotoscopic peripalpebral purpura
- Carpal tunnel syndrome
- Subcutaneous nodules

**Testing**
The International Myeloma Workshop guidelines for standard investigative workup in patients with suspected MM include the following[1]:

Serum and urine assessment for monoclonal protein (densitometer tracing and nephelometric quantitation; immunofixation for confirmation)
- Serum free light chain assay (in all patients with newly diagnosed plasma cell dyscrasias)
- Bone marrow aspiration and/or biopsy
- Serum beta2-microglobulin, albumin, and lactate dehydrogenase measurement
- Standard metaphase cytogenetics
- Fluorescence in situ hybridization
- Skeletal survey

MRI
Routine laboratory tests include the follow-
ing:
• Complete blood count and differential
• Erythrocyte sedimentation rate
• Comprehensive metabolic panel (eg, levels of total protein, albumin and globulin, BUN, creatinine, uric acid)
• 24-hour urine collection for quantification of the Bence Jones protein (ie, lambda light chains), protein, and creatinine clearance; proteinuria greater than 1 g of protein in 24 hours is a major criterion

C-reactive protein
Serum viscosity in patients with CNS symptoms, nosebleeds, or very high M protein levels

Imaging studies
Simple radiography for the evaluation of skeleton lesions; skeletal survey, including the skull, long bones, and spine.

MRI for detecting thoracic and lumbar spine lesions, paraspinal involvement, and early cord compression.

PET scanning in conjunction with MRI potentially useful.

• Differential Diagnoses
• Malignant Lymphoma
• Metastatic Bone Disease
• Monoclonal Gammapathies of Undetermined Significance
• Waldenstrom Macroglobulinemia

Management
There is currently no cure for MM. However, advances in therapy, such as autologous stem cell transplantation, radiation, and surgical care in certain cases, have helped to lessen the occurrence and severity of adverse effects of this disease and to manage associated complications.[3, 4, 5]

Chemotherapy and immunosuppression
Several drug therapies are valuable in the treatment of symptomatic MM. Clinicians treat many patients with high-dose therapy and peripheral blood or bone marrow stem cell transplantation.

Chemotherapy regimens used in patients with MM include the following:

Thalidomide, either as a single agent or in combination with steroids or with melphalan
• Lenalidomide plus dexamethasone
• Bortezomib plus melphalan
• VAD (vincristine, doxorubicin [Adriamycin], and dexamethasone)
• Melphalan plus prednisone

The 2016 NCCN guidelines for MM list the following combinations as preferred regimens (category 1) for primary induction therapy in transplant candidates[2] :
• Bortezomib/dexamethasone
• Bortezomib/doxorubicin/dexamethasone
• Bortezomib/thalidomide/dexamethasone
• Lenalidomide/dexamethasone

The 2016 National Comprehensive Cancer Network (NCCN) guidelines for MM list the following combinations as preferred regimens for primary induction therapy in patients who are not transplant candidates[2] :

Bortezomib/dexamethasone
• Bortezomib/cyclophosphamide/dexamethasone
• Bortezomib/lenalidomide/dexamethasone (category 1)
• Lenalidomide/low-dose dexamethasone
Patients with refractory disease or relapse may be treated with the following:

Any of the agents not previously used

- Bortezomib plus cyclophosphamide and dexamethasone [2, 6]
- Carfilzomib (Kyprolis)
- Thalidomide
- Lenalidomide plus cyclophosphamide and dexamethasone [2]
- Pomalidomide [7, 8]

References