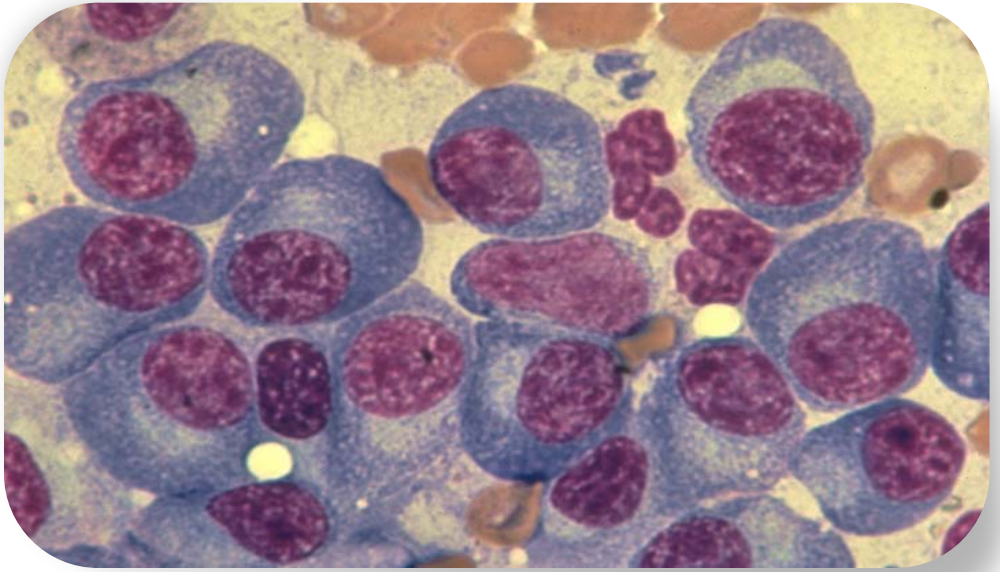
MULTIPLE MYELOMA



Dr.Jobin Alex Mohan

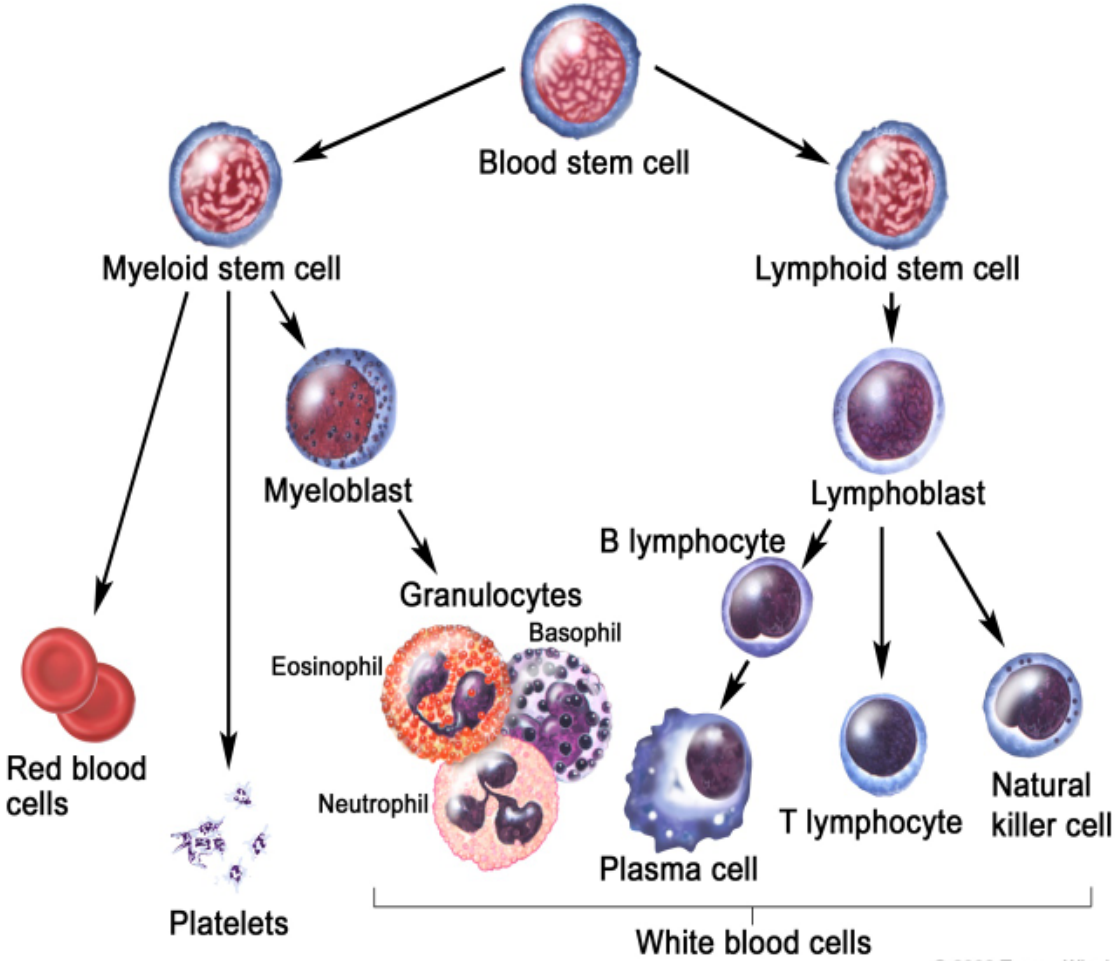
- **Multiple myeloma** (from Greek *myelo-*, bone marrow), also known as **plasma cell myeloma** or **Kahler's disease** (after Otto Kahler)

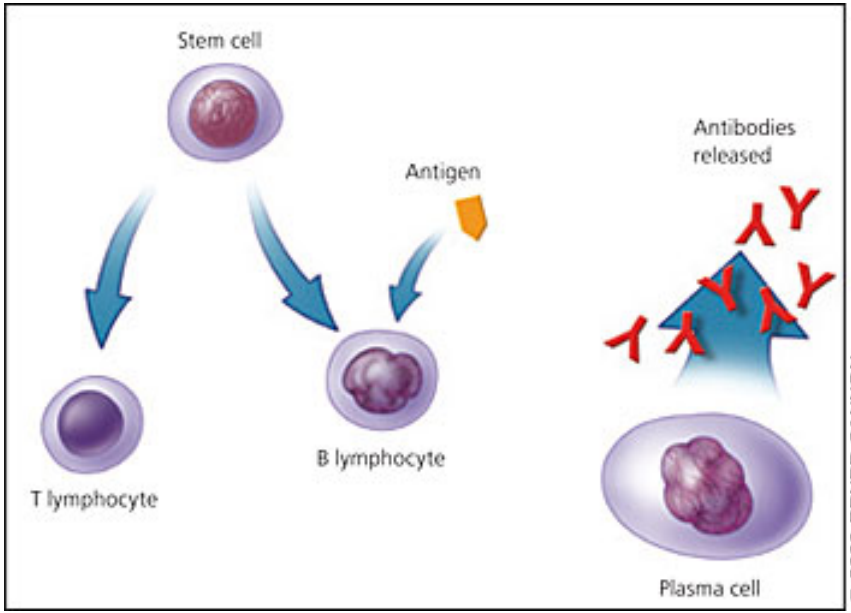
- Multiple myeloma (MM) is a debilitating malignancy that is part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance(MGUS) to plasma cell leukemia.

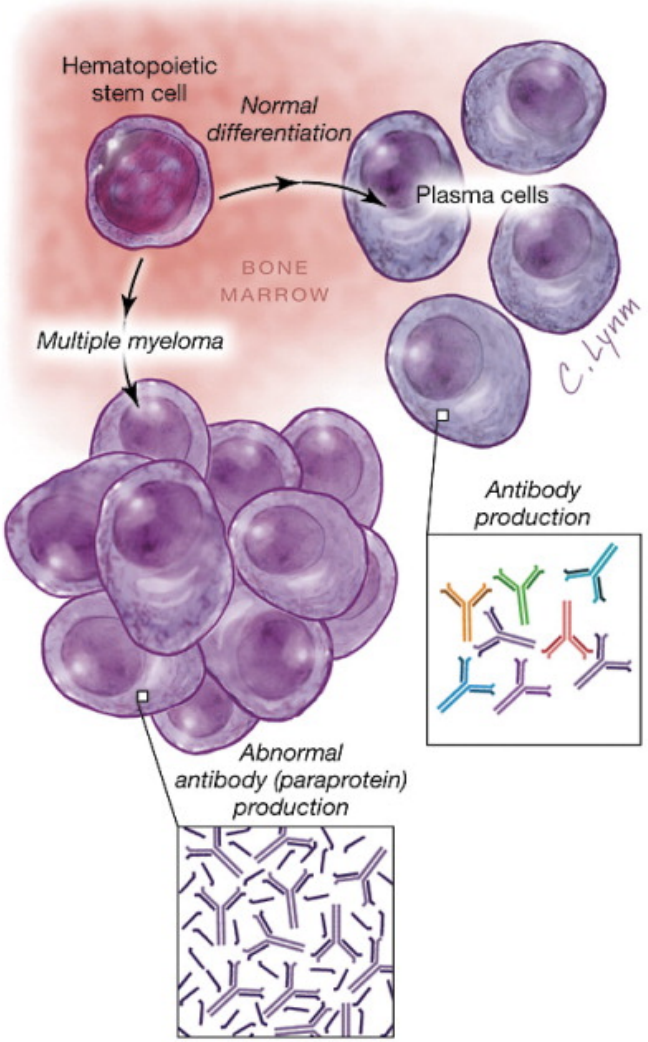
- *First described in 1848, MM is characterized by a proliferation of malignant plasma cells and a subsequent overabundance of monoclonal paraprotein (M protein).*

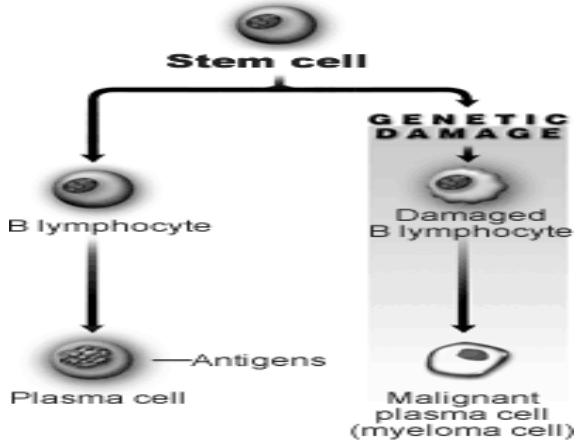
- Myeloma is a malignancy of the plasma cell.
- Plasma cells produce immunoglobulins, which are commonly called antibodies.
- There are literally thousands of different antibodies, each consisting of pairs of heavy and light chains.
- Antibodies are typically grouped into five types: IgA, IgD, IgE, IgG, and IgM.

 When someone contracts myeloma, a malignant clone, a rogue plasma cell, reproduces in an uncontrolled fashion, resulting in overproduction of the specific antibody that it was designed to produce.



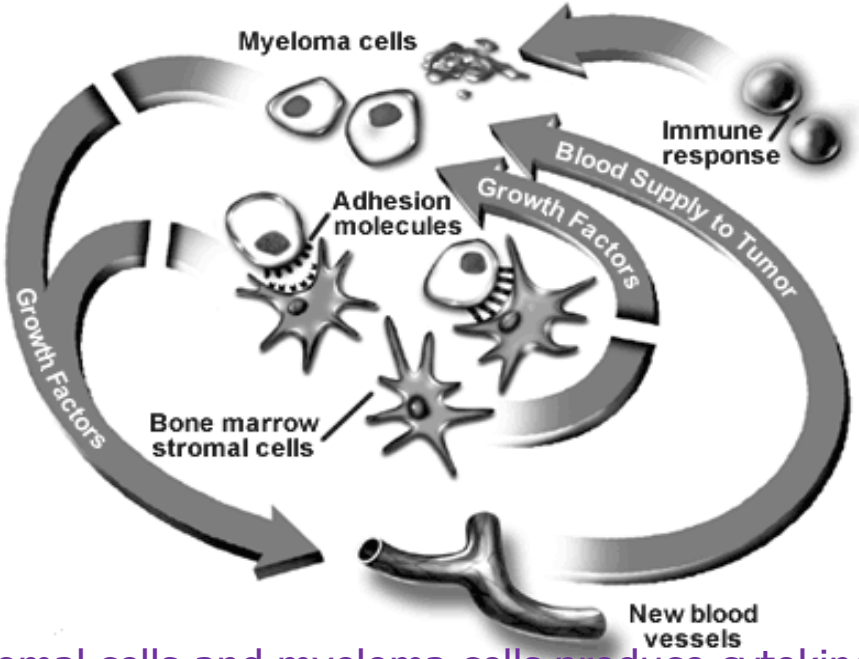

Stem cell
Antigen
Antibodies released
T lymphocyte
B lymphocyte
Plasma cell
© 2008 RENEE CANNON





In multiple myeloma, the B cell is damaged and gives rise to too many plasma cells (myeloma cells).

These malignant cells do not function properly and their increased numbers produce excess immunoglobulins of a single type that the body does not need along with reduced amounts of normal immunoglobulins.



Bone marrow stromal cells and myeloma cells produce cytokines that help myeloma cells grow and survive.

Myeloma cells also produce growth factors that stimulate new blood vessel formation through a process called angiogenesis.

New blood vessels provide nutrients and oxygen to the tumor, allowing it to grow. The natural immune response that attacks myeloma cells is suppressed.

- Each type of antibody has a different number of light chain and heavy chain pairs.

- As a result, there is a characteristic normal distribution of plasma cells in the blood by molecular weight.

- When there is a malignant clone, there is usually overproduction of a single antibody, resulting in a "spike" on the normal distribution, which is called an M spike (or monoclonal spike).

- People will sometimes develop a condition called MGUS (Monoclonal gammopathy of undetermined significance), where there is overproduction of one antibody but the condition is benign (does not threaten the patient's health).

MGUS & MM DIFF-

In MGUS

- Levels of antibody are lower
- Number of plasma cells in the BM is lower
- No symptoms or problems
- No treatment is indicated

Epidemiology

- Elderly (mean age 68 years).
- How common
  - 5/100,000
- Twice as common in black persons
- Men > Women
- Family History = 4 fold increased risk (autosomal dominant)
- Associated conditions: Obesity, RA, MGUS

- Occupational Exposures:
  - Ionizing radiation
  - Farming pesticides,
  - Petroleum Workers.

- A variety of chromosomal alterations - most common translocations are t(11;14)(q13;q32) and t(4;14)(p16;q32),

- Mutations in p53 and Rb-1 have also been described.

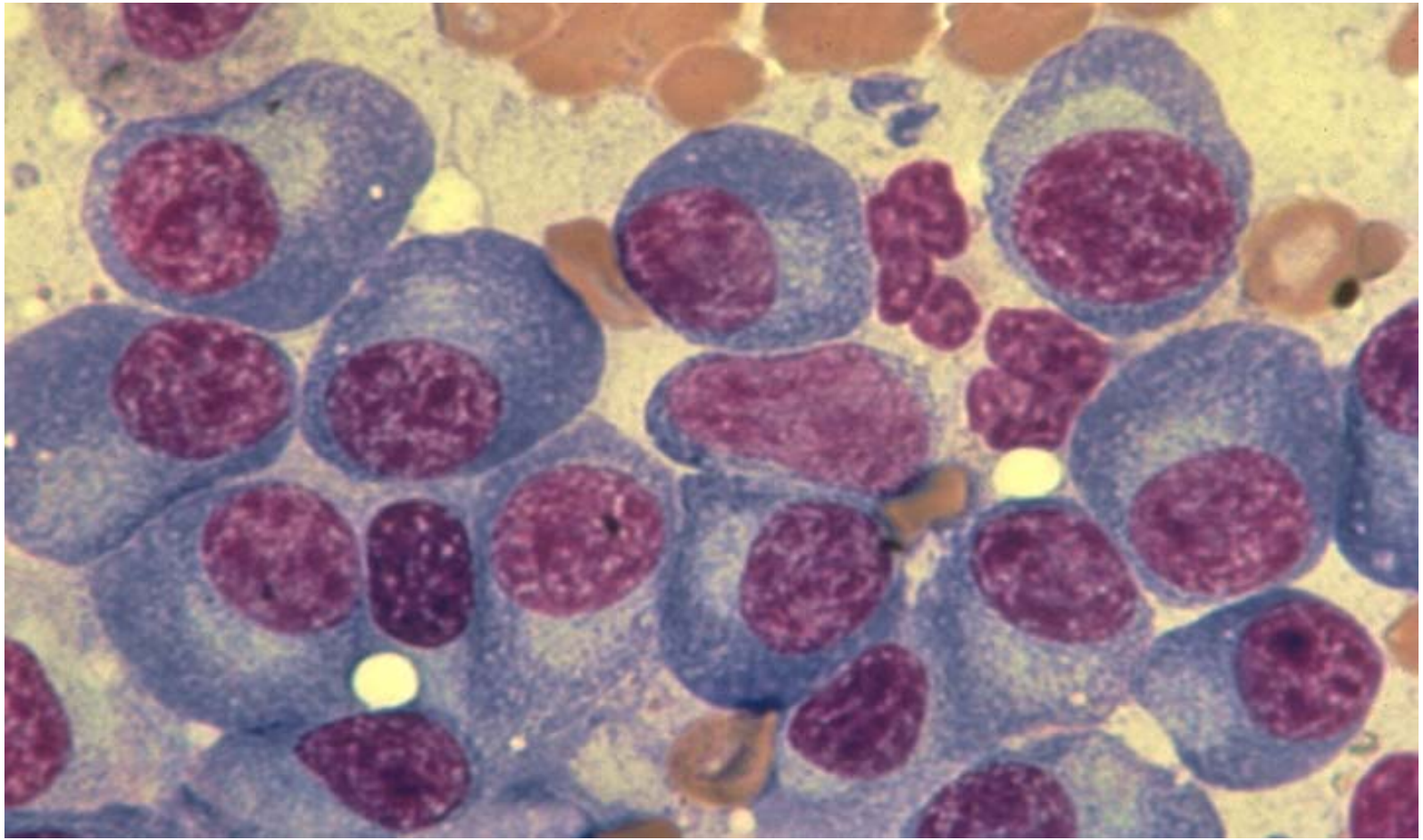
PATHOPHYSIOLOGY

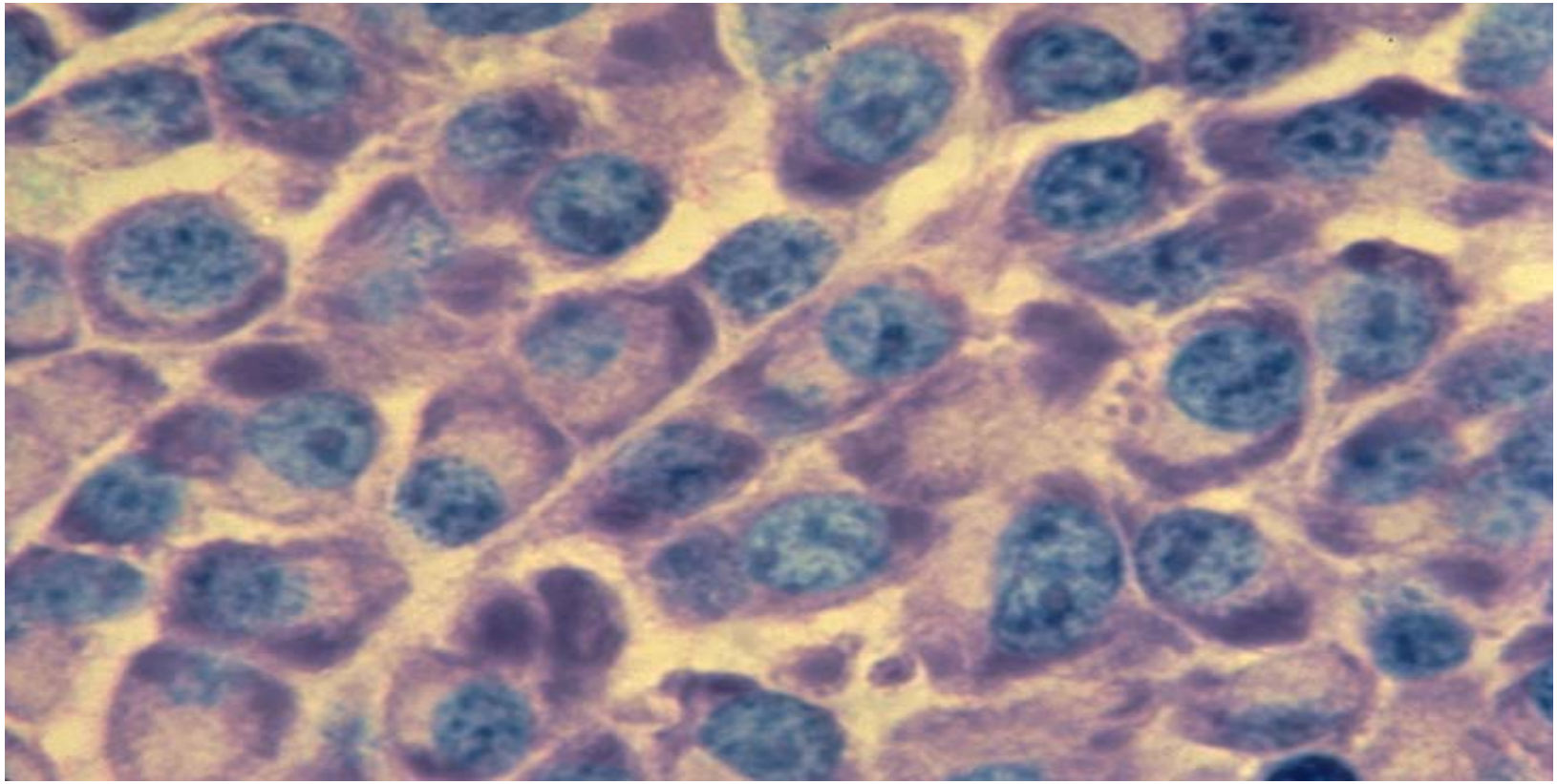
- MM is characterized by neoplastic proliferation of plasma cells involving more than 10% of the bone marrow

- 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
- 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-1b.

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

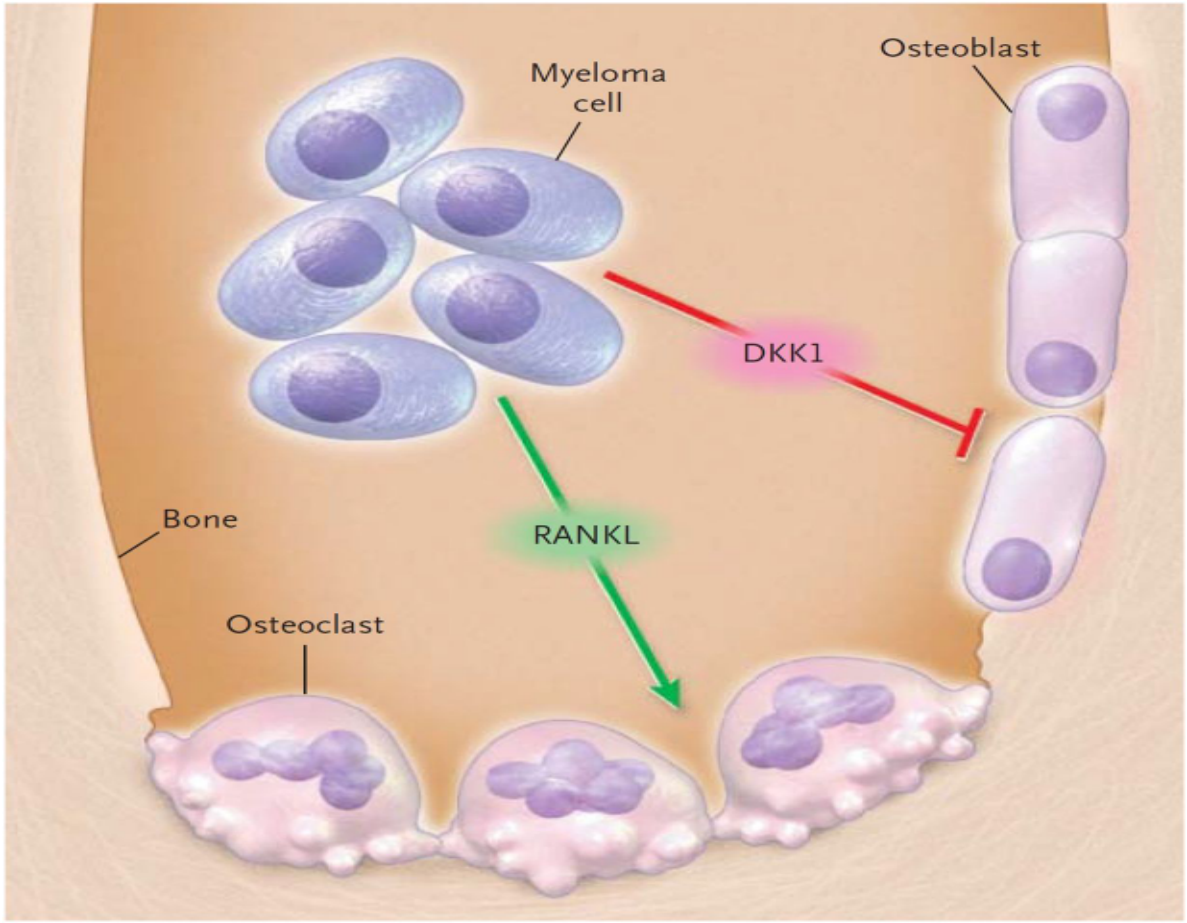
- Isolated plasmacytomas (which affect 2-10% of patients) lead to hypercalcemia through production of the osteoclast-

- 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.

DUAL MECHANISMS OF BONE LOSS- MM



Myeloma cells release

RANK ligand (RANKL), stimulating osteoclasts,

Dickkopf 1 (DKK1), a protein that inhibits osteoblastic function

Leads to **loss of osteoblastic differentiation** & **destruction of osteoblast-lineage stem cells**

Resulting in lytic bone lesions that cannot heal.

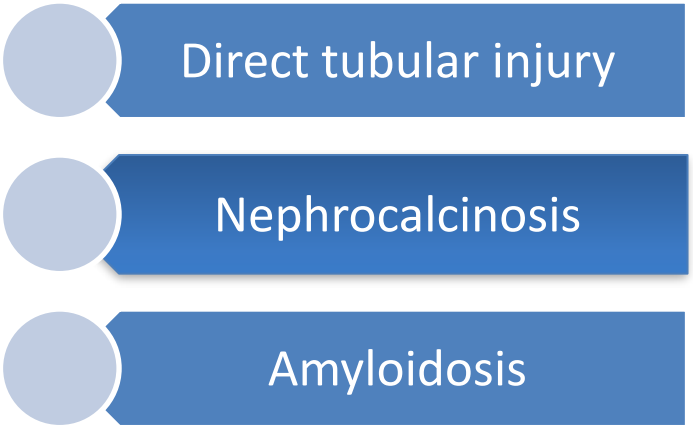
Hematologic processes

- 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



- 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.

Genetic causes

- MM has been reported in 2 or more first-degree relatives and in identical twins, although no evidence suggests a hereditary basis for the disease.

- abnormalities of certain oncogenes, such as *c-myc*, are associated with development early in the course of plasma cell tumors

- abnormalities of oncogenes such as *N-ras* and *K-ras* are associated with development after bone marrow relapse.

- Abnormalities of tumor suppressor genes, such as *TP53*, have been shown to be associated with spread to other organs.

- Ongoing research is investigating whether human leukocyte antigen (HLA)-Cw5 or HLA-Cw2 may play a role in the pathogenesis of multiple myeloma.

Environmental or occupational causes

- ndividuals with significant exposures in the agriculture, food, and petrochemical industries.

MGUS

- Approximately 19% of patients with MGUS develop MM within 2-19 years.

Radiation

- Radiation may play a role in some patients.

Chronic inflammation

- A relationship between MM and preexisting chronic inflammatory diseases has been suggested. However, a case-control study provides no support for the role of chronic antigenic stimulation.

Infection

- Human herpesvirus 8 (HPV8) infection of bone marrow dendritic cells was found in patients with MM and in some patients with MGUS.

History

- Presenting symptoms of multiple myeloma (MM) include bone pain, pathologic fractures, weakness, anemia, infection (often pneumococcal), hypercalcemia, spinal cord compression, or renal failure.
- The diagnosis is incidental in 30% of cases.
- MM is often discovered through routine blood screening when patients are being evaluated for unrelated problems.
- Typically, a large gap between the total protein and the albumin levels observed on an automated chemistry panel suggests a problem (ie, protein minus albumin equals globulin).

- In one third of patients, MM is diagnosed after a pathologic fracture occurs; such fractures commonly involve the axial skeleton.

- Two thirds of patients complain of bone pain, commonly with lower back pain. This bone pain is frequently located in the back, long bones, skull, and/or pelvis.

- Patients may also complain of nonspecific constitutional symptoms related to hyperviscosity and hypercalcemia.

- **Bone pain**
- Bone pain is the most common presenting symptom in MM. Most case series report that 70% of patients have bone pain at presentation. The lumbar spine is one of the most common sites of pain.

- **Pathologic fractures and bone lesions**
- Pathologic fractures are very common in MM; 93% of patients have more than one site of bony involvement. A severe bony event is a common presenting issue.

- **Spinal cord compression**
- The symptoms that should alert physicians to consider spinal cord compression are back pain, weakness, numbness, or dysesthesias in the extremities. Because spinal cord compressions in MM occur at multiple levels, comprehensive evaluation of the spine is warranted. Patients who are ambulatory at the start of therapy have the best likelihood of preserving function and avoiding paralysis.

- **Bleeding**
- Occasionally, a patient may come to medical attention for bleeding resulting from thrombocytopenia. Rarely, monoclonal protein may absorb clotting factors and lead to bleeding.

- **Hypercalcemia**
- Confusion, somnolence, bone pain, constipation, nausea, and thirst are the presenting symptoms of hypercalcemia. This complication may be present in as many as 30% of patients with MM at presentation. In most solid malignancies, hypercalcemia carries an ominous prognosis, but in MM, its occurrence does not adversely affect survival.

- **Infection**
- Abnormal humoral immunity and leukopenia may lead to infection. Pneumococcal organisms are commonly involved, but shingles (ie, herpes zoster) and *Haemophilus* infections are also more common among patients with MM.

- **Hyperviscosity**

- Hyperviscosity may be associated with a number of symptoms, including, generalized malaise, infection, fever, paresthesia, sluggish mentation, and sensory loss.

- Patients may report headaches and somnolence, and they may bruise easily and have hazy vision

- Patients with MM typically experience these symptoms when their serum viscosity is greater than 4 times that of normal serum.

- Epistaxis may be a presenting symptom of MM with a high tumor volume. Occasionally, patients may have such a high volume of monoclonal protein that their blood viscosity increases, resulting in complications such as stroke, myocardial ischemia, or infarction.

- **Neurologic symptoms**
- Carpal tunnel syndrome is a common complication of myeloma.
- Meningitis (especially that resulting from pneumococcal or meningococcal infection) is more common in patients with MM. Some peripheral neuropathies have been attributed to MM.
- Long-term neurologic function is directly related to the rapidity of the diagnosis and the institution of appropriate therapy for MM.

- **Anemia**
- Anemia, which may be quite severe, is the most common cause of weakness in patients with MM.

Red Flags for Potential Diagnosis of Multiple Myeloma in Patients with Back Pain

Age over 50 years

Pain that is worse in supine position

Pain that is worse at night or awakens patient from sleep

Pain with a band-like distribution around the body

Pain that is not relieved with conventional methods (i.e., rest, nonsteroidal anti-inflammatory drugs, acetaminophen [Tylenol])

Associated constitutional symptoms (fever, weight loss, dehydration)

Progressive neurologic deficit in lower extremities

Clinical Manifestations of Multiple Myeloma

- Pain in the lower back, long bones or ribs
- Generalized malaise
- Infections
- Fever
- Bleeding
- Symptoms of hypercalcemia
  - Nausea
  - Fatigue
  - Thirst
- Symptoms of hyperviscosity
  - Headaches
  - Bruising
  - Ischemic neurologic symptoms
- Other neurologic symptoms
  - Peripheral neuropathy
  - Meningitis

PHYSICAL EXAMINATION

- On head, ears, eyes, nose, and throat (HEENT) examination, the eyes may show exudative macular detachment, retinal hemorrhage, or cotton-wool spots.

- Pallor from anemia may be present. Ecchymoses or purpura from thrombocytopenia may be evident.

- Bony tenderness is not uncommon in MM, resulting from focal lytic destructive bone lesions or pathologic fracture. Pain without tenderness is typical.

- Pathologic fractures may be observed.

- In general, painful lesions that involve at least 50% of the cortical diameter of a long bone or lesions that involve the femoral neck or calcar femorale are at high (50%) risk for a pathologic fracture.

- The risk of fracture is lower in upper-extremity lesions than in lower-extremity lesions. Even a small cortical defect can decrease torsional strength by as much as 60% (stress riser effect).

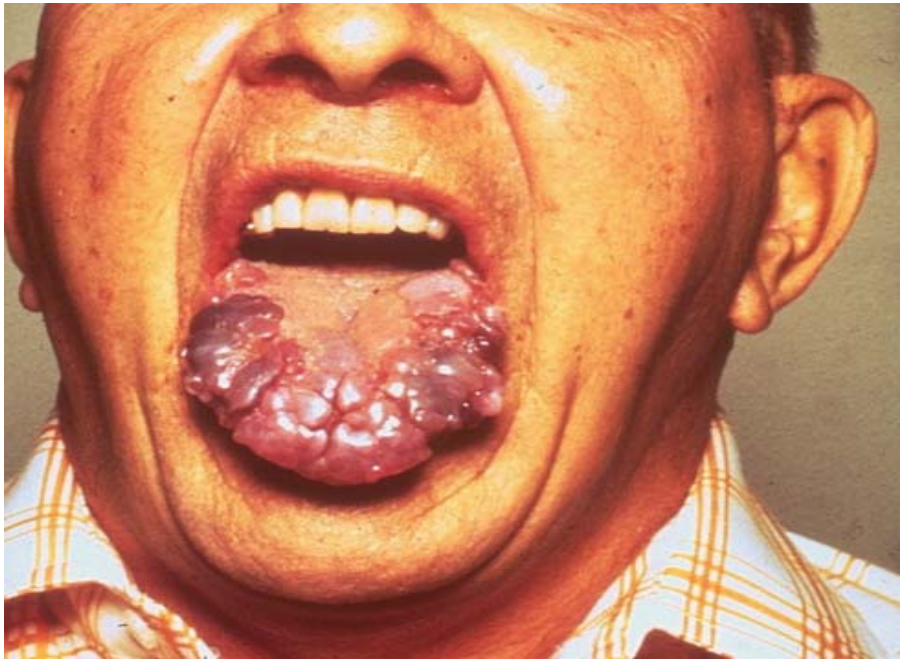
- Neurologic findings may include a sensory level change (ie, loss of sensation below a dermatome corresponding to a spinal cord compression), neuropathy, myopathy, a Tinel sign, or a Phalen sign due to carpel tunnel compression secondary to amyloid deposition.

- Extramedullary plasmacytomas, which consist of soft-tissue masses of plasma cells, are not uncommon. Plasmacytomas have been described in almost every site in the body. Although the aerodigestive tract is the most common location, reports also describe orbital, ear canal, cutaneous, gastric, rectal, prostatic, and retroperitoneal lesions.

- On evaluation of the abdomen, hepatosplenomegaly may be discovered. Cardiovascular system examination may reveal cardiomegaly secondary to immunoglobulin deposition.

- Amyloidosis may develop in some patients with MM.
- The characteristic physical examination findings that suggest amyloidosis include the following:
- Shoulder pad sign
- Macroglossia
- Typical skin lesions
- Postprotoscopic peripalpebral purpura
- The shoulder pad sign is defined by bilateral swelling of the shoulder joints secondary to amyloid deposition. Physicians describe the swelling as hard and rubbery. Amyloidosis may also be associated with carpal tunnel syndrome and subcutaneous nodules.
- Macroglossia may occur secondary to amyloid deposition in the tongue and is a common finding in patients with amyloidosis

- Macroglossia may occur secondary to amyloid deposition in the tongue and is a common finding in patients with amyloidosis

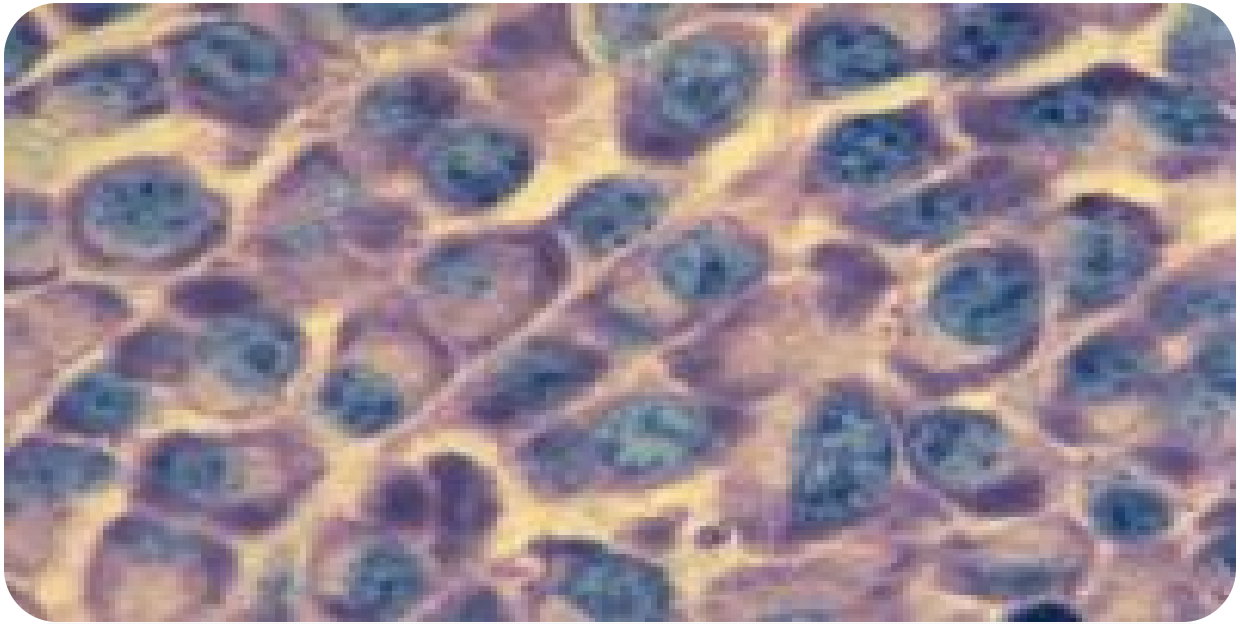


WORK UP -APPROACH CONSIDERATIONS

- Consider the risk of renal failure, especially in the setting of contrast medium injection for imaging studies. Take care to limit patients' exposure and maintain hydration.

- The 2009 International Myeloma Workshop developed guidelines for standard investigative workup in patients suspected to have multiple myeloma. These guidelines included the following:[1]

1. Serum and urine assessment for monoclonal protein (densitometer tracing and nephelometric quantitation; immunofixation for confirmation)
2. Serum-free light chain assay (in all patients with newly diagnosed plasma cell dyscrasias)
3. Bone marrow aspiration and/or biopsy
4. Serum beta(2)-microglobulin, albumin, and lactate dehydrogenase measurement
5. Standard metaphase cytogenetics
6. Fluorescent in situ hybridization
7. Skeletal survey
8. MRI



Bone marrow biopsy : sheets of malignant plasma cells in MM

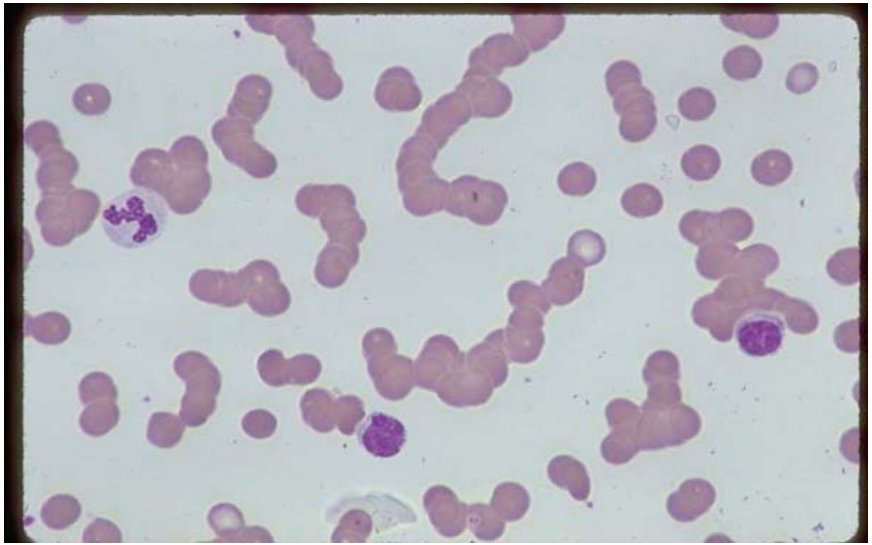
- **Complete Blood Count**

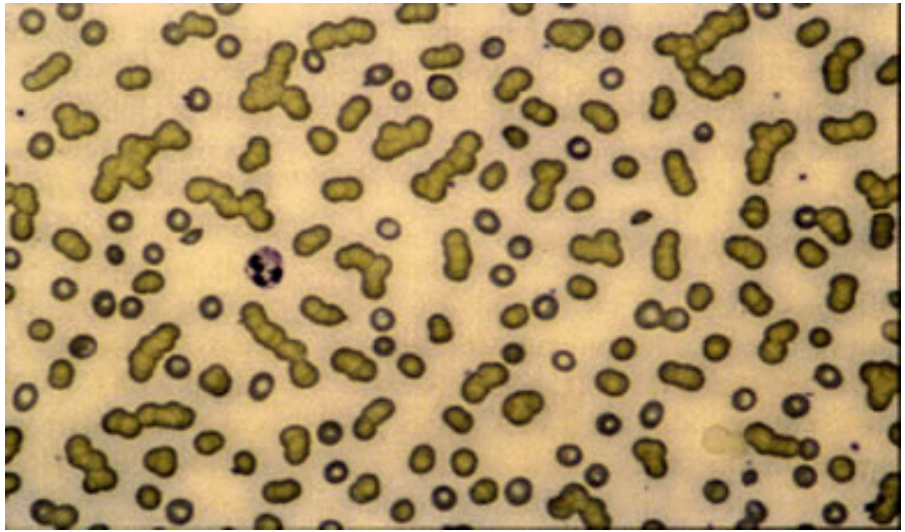
- Perform a complete blood count (CBC) to determine if the patient has anemia, thrombocytopenia, or leukopenia.

- The CBC and differential may show pancytopenia, abnormal coagulation, and an increased erythrocyte sedimentation rate (ESR).

- The reticulocyte count is typically low.

- Peripheral blood smears may show Rouleau formation.





Rouleaux formation : high plasma protein

- **Metabolic Panel**
- Obtain a comprehensive metabolic panel to assess levels of total protein, albumin and globulin, blood urea nitrogen (BUN), creatinine, and uric acid (uric acid will be high if the patient has high cell turnover or is dehydrated).

- **Urine Collection**
- Obtain a 24-hour urine collection for quantification of the Bence Jones protein (ie, lambda light chains), protein, and creatinine clearance. Quantification of proteinuria is useful for the diagnosis of MM (>1 g of protein in 24 h is a major criterion) and for monitoring the response to therapy. Creatinine clearance can be useful for defining the severity of the patient’s renal impairment.

- **Electrophoresis and Immunofixation**

- Serum protein electrophoresis (SPEP) is used to determine the type of each protein present and may indicate a characteristic curve (ie, where the spike is observed).

- Urine protein electrophoresis (UPEP) is used to identify the presence of the Bence Jones protein in urine. Immunofixation is used to identify the subtype of protein (ie, IgA lambda).

- The 2011 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Oncology, Multiple Myeloma Version recommend the use of serum free light chain assay as well as fluorescence in situ hybridization (FISH) for 1q21 amplification as part of the initial diagnostic workup.

- Chemical screening, including calcium and creatinine SPEP, immunofixation, and immunoglobulin quantitation, may show azotemia, hypercalcemia, an elevated alkaline phosphatase level, and hypoalbuminemia. A high lactic dehydrogenase (LDH) level is predictive of an aggressive lymphomalike course.

- SPEP is a useful screening test for detecting M proteins. An M component is usually detected by means of high-resolution SPEP. The kappa-to-lambda ratio has been recommended as a screening tool for detecting M-component abnormalities. An M-component serum concentration of 30 g/L is a minimal diagnostic criterion for MM. In about 25% of patients, M protein cannot be detected by using SPEP.

- Routine urinalysis may not indicate the presence of Bence Jones proteinuria. Therefore, a 24-hour urinalysis by means of UPEP or immunoelectrophoresis may be required. UPEP or immunoelectrophoresis can also be used to detect an M component and kappa or lambda light chains. The most important means of detecting MM is electrophoretic measurement of immunoglobulins in both serum and urine.

- **Quantitative Immunoglobulin Levels (IgG, IgA, IgM)**

- Suppression of nonmyelomatous immunoglobulin is a minor diagnostic criterion for MM.
- The level of MM protein (ie, M protein level), as documented by the immunoglobulin level, can be useful as a marker to assess the response to therapy.

Beta-2 Microglobulin

- Beta-2 microglobulin is a surrogate marker for the overall body tumor burden.
- The level of beta-2 microglobulin is increased in patients with renal insufficiency without MM, which is one reason that it is a useful prognosticator in MM.

- **C-Reactive Protein ESR**

- C-reactive protein (CRP) is a surrogate marker of interleukin (IL)-6 activity. IL-6 is often referred to as the plasma cell growth factor. Like beta-2 microglobulin, CRP is useful for prognostication.

- **Serum Viscosity**
- Check the serum viscosity in patients with central nervous system (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

D IAGNOSTIC *C* RITERIA

- **Durie-Salmon criteria**

Dx : 1 major & 1 minor or 3 minor criteria

Major criteria

- Plasmacytoma on tissure biopsy
- BM plasmacytosis with > 30% plasma cell
- Monoclonal globulin spike on serum electrophoresis 3.5 g/dl for Ig G ,> 2g/dl for IgA
- Or urine Bence Jones > 1g/24 hr

Minor criteria

- Marrow plasmacytosis 10-29 %
- Monoclonal globulin spike present ,but less than above
- Lytic bone lesion
- Normal Ig M< 0.05g/dl , IgA <0.1g/dl , IgG<0.6 g/dl

- In 2003, the International Myeloma Working Group agreed on diagnostic criteria for symptomatic myeloma, asymptomatic myeloma and MGUS (monoclonal gammopathy of undetermined significance), which was subsequently updated in 2009

- Symptomatic myeloma:
  - Clonal plasma cells >10% on bone marrow biopsy or (in any quantity) in a biopsy from other tissues (plasmacytoma)
  - A monoclonal protein (paraprotein) in either serum or urine (except in cases of true non-secretory myeloma)
  - Evidence of end-organ damage felt related to the plasma cell disorder (*related organ or tissue impairment*, ROTI, commonly referred to by the acronym "CRAB"):
    - Hyper**C**alcemia (corrected calcium >2.75 mmol/L)
    - **R**enal insufficiency attributable to myeloma
    - **A**nemia (hemoglobin <10 g/dL)
    - **B**one lesions (lytic lesions or osteoporosis with compression fractures)

- Asymptomatic (smoldering) myeloma:

- Serum paraprotein >30 g/L AND/OR
- Clonal plasma cells >10% on bone marrow biopsy AND
- NO myeloma-related organ or tissue impairment

- Monoclonal gammopathy of undetermined significance (MGUS):

- Serum paraprotein <30 g/L AND
- Clonal plasma cells <10% on bone marrow biopsy AND
- NO myeloma-related organ or tissue impairment

- **The International Staging System (ISS)**

  - Stage I : β2-microglobulin (β2M) < 3.5 mg/L, albumin >= 3.5 g/dL
  - Stage II : β2M < 3.5 and albumin < 3.5; or β2M between 3.5 and 5.5
  - Stage III : β2M > 5.5

Differential Diagnosis of Multiple Myeloma

Disease	*Distinctive features*
MGUS	M protein < 3 g per dL (30 g per L), < 10% plasma cell in bone marrow, no urine M protein, no lytic lesions, anemia, hypercalcemia or renal disease
SMM	M protein > 3 g per dL (30 g per L), > 10% plasma cell in bone marrow, no lytic lesions, no anemia, hypercalcemia or renal disease
PCL	> 20% plasma cell in peripheral blood, small levels of M protein, few bone lesions, few hematologic disturbances; younger population
SP	Only one tumor with no other bone lesions, urine or serum abnormalities
WM	IgM M protein, hyperviscosity, hypercellular bone marrow with extensive infiltration by lymphoplasma cells
HCD	M protein with an incomplete heavy chain lacking a light chain

MGUS = monoclonal gammopathy of undetermined significance; SMM = smoldering multiple myeloma; PCL = plasma cell leukemia; SP = solitary plasmacytoma; WM = Waldenstrom macroglobulinemia; HCD = heavy chain disease.

Solitary Plasmacytoma

- plasma cell tumor occurring in a single skeletal location and lacking appropriate criteria for diagnosis of multiple myeloma
- sensitive to radiation
- progress to multiple myeloma in over 50% of patients
- diagnostic criteria
  - solitary lesion on skeletal survey
  - histologic biopsy confirmation of plasmacytoma
  - negative bone marrow biopsy (i.e. no plasma cells in bone marrow)

- **Osteosclerotic Myeloma** rare syndrome characterized by
- POEMS: Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin changes
- neurologic symptoms are symmetric and begin distal and migrate proximally
  - sensory symptoms manifest first and then are followed by motor weakness
  - neurological symptoms usually do not improve
- skin lesions are characteristic and occur predominantly in the trunk
  - up to 25-50% of skin lesions occur in the extremities
- sclerotic bone lesions occur in both the axial and appendicular skeleton

THANK YOU