Plasma Cell Neoplasms

Plasma cell neoplasms: definition

- Immunosecretory disorders result from the expansion of a single clone of immunoglobulin secreting, terminally differentiated, end-stage B-cells.
- These monoclonal proliferations of either plasma cells or plasmocytoid lymphocytes are characterised by secretion of a single homogeneous immunoglobulin product known as the M-component or monoclonal component.

Plasma cell neoplasms: definition

- The prominence of the M-component in serum and urine protein electrophoresis (SPE, UPE) has led to various designations for these disorders including monoclonal gammopathies, dysproteinemias and paraproteinemias.
- The M-components, although monoclonal, may be seen in both malignant conditions (plasma cell myeloma and Waldenström macroglobulinemia) and benign or premalignant disorders (MGUS).

Plasma cell neoplasms: definition

- Among these gammopathies are a number of clinicopathological entities, some being primarily plasmacytic, including plasma cell (multiple) myeloma and plasmacytoma; while others contain also lymphocytes, including the heavy chain diseases and Waldenström macroglobulinemia.

Plasma cell neoplasms: definition

- Variants of plasma cell myeloma include syndromes defined by the consequence of tissue immunoglobulin deposition, including (1) primary amyloidosis (AL), and (2) light and heavy chain deposition diseases.

Plasma Cell Myeloma

Plasma Cell Myeloma: Definition

- Bone marrow based, multifocal plasma cell neoplasm characterised by a serum monoclonal protein and skeletal destruction with osteolytic lesions, pathological fractures, bone pain, hypercalcemia, and anemia.
- The disease spans a spectrum from localized, smoldering or indolent to aggressive, disseminated forms with plasma cell infiltration of various organs, plasma cell leukemia and deposition of abnormal Ig chains in tissues.

Plasma Cell Myeloma: Definition

- The diagnosis is based on a combination of pathological, radiological, and clinical features.
- Synonyms: Multiple myeloma, Myelomatosis, Medullary plasmacytoma, Kahler´s disease.

WHO criteria for the diagnosis of Symptomatic Plasma Cell Myeloma

- Bone marrow clonal plasma cells (usu >10%) or plasmacytoma on biopsy
- Presence of a monoclonal protein (M-component) in serum or urine; usu
  IgG>30 g/L, IgA >25 g/L or urine light chain >1 g/24 hr
- Related organ or tissue impairment (CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions)

WHO criteria for the diagnosis of Asymptomatic (smoldering) myeloma:

- Presence of a monoclonal protein (M-component) in serum
  IgG>30 g/L, IgA >25 g/L

  AND/OR: Clonal plasma cells in BM >10%

- No related organ impairment (no CRAB)

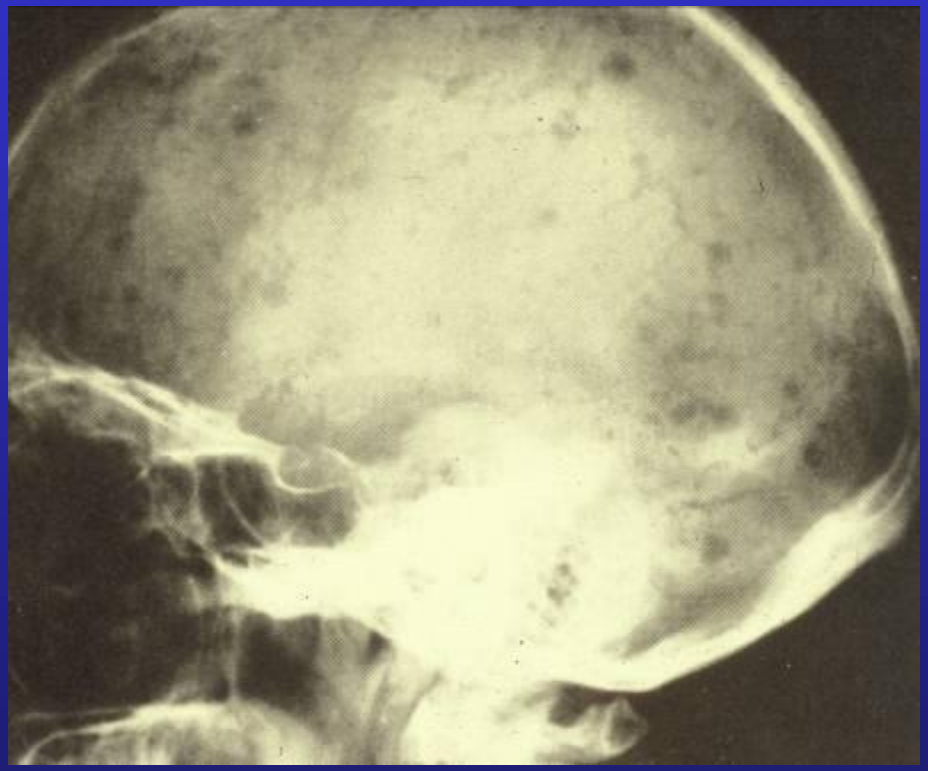
Epidemiology

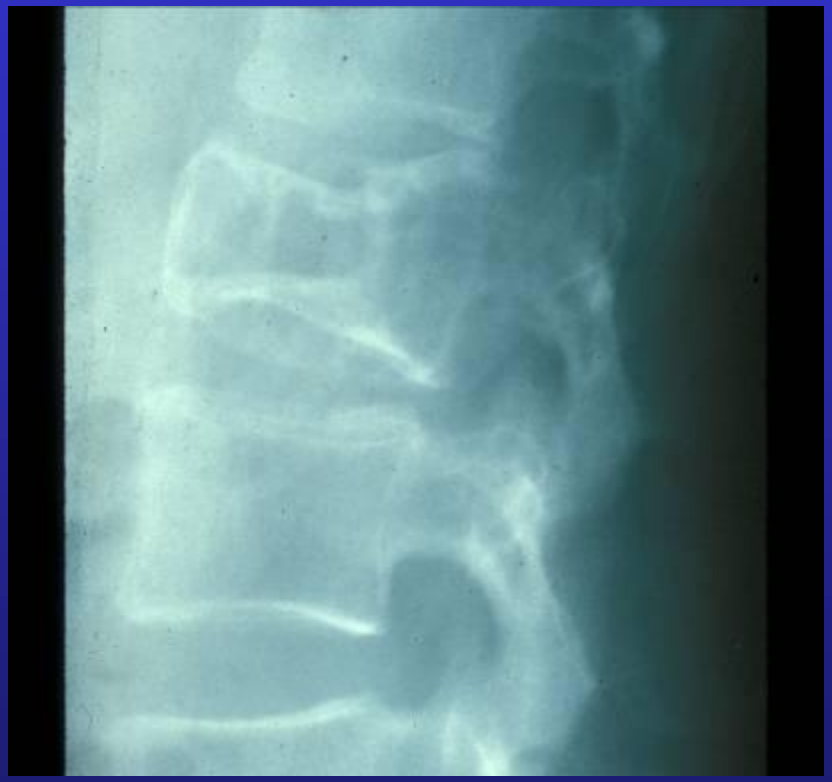
- In USA, plasma cell myeloma is the most common malignancy in Blacks and the second most common in Whites, representing 15% of all hematological malignancies.
- The higher incidence in Blacks mirrors their higher physiologic Ig level, suggesting a larger B-cell population at risk of malignant change.
- In 2007 in US: 20,000 new cases; 10,000 died of the disease
- Median age at diagnosis is 68 in males and 70 in females. M:F ratio is 1:4.

Sites of involvement

- Generalized BM involvement is typically present.
- Lytic bone lesions and tumor masses of plasma cells also occur. The most common sites are in marrow areas of most active hematopoiesis, including in order of frequency: the vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula.

Lytic lesions (punched out lesions) on X Ray





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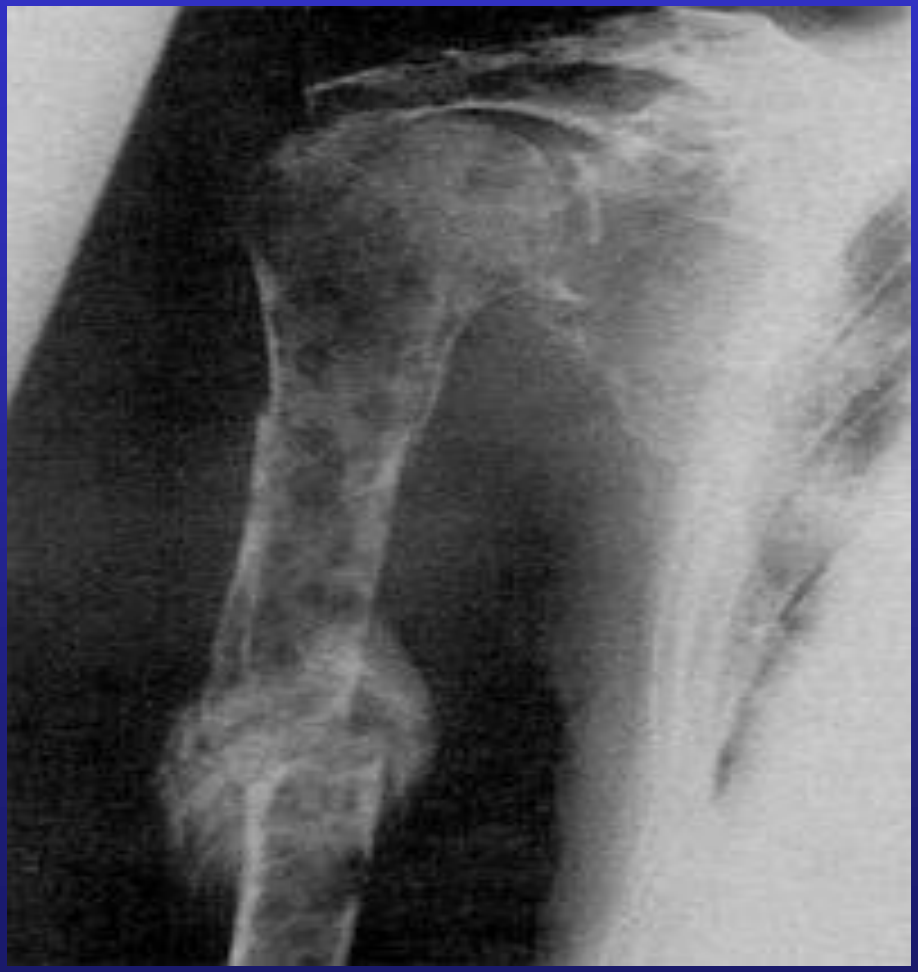
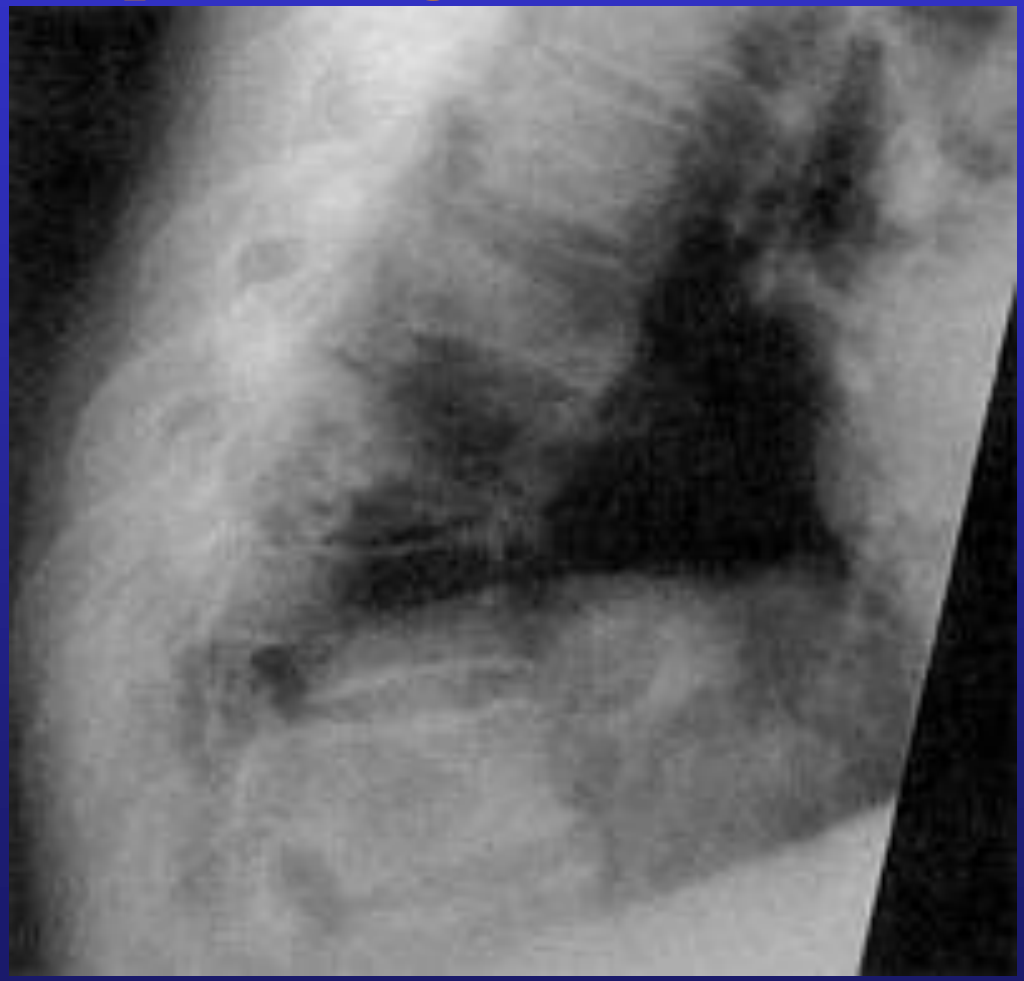


Vertebral collapse secondary to pathological fracture



Clinical features

- A constellation of radiological, clinical, laboratory and pathological findings are combined to provide diagnostic criteria.
- The extensive skeletal destruction results in bone pain, pathological fractures, hypercalcemia and anemia.
- Recurrent bacterial infections and renal insufficiency are common.

Clinical features

- The infections are in part a consequence of depressed normal Ig production due to displacement by the neoplastic clone.
- Renal failure follows the tubular damage resulting from monoclonal light chain proteinuria.
- Anemia is due both to marrow replacement and renal damage with resultant loss of erythropoietin.

Clinical features

- An M-component is found in the serum or urine in 99% of pts.
- The serum protein electrophoretic pattern shows a peak or localized band in 80% of pats.
- In most pts there is hypogammaglobulinemia (>50% reduction in normal serum Ig); rarely a normal Ig profile is seen.

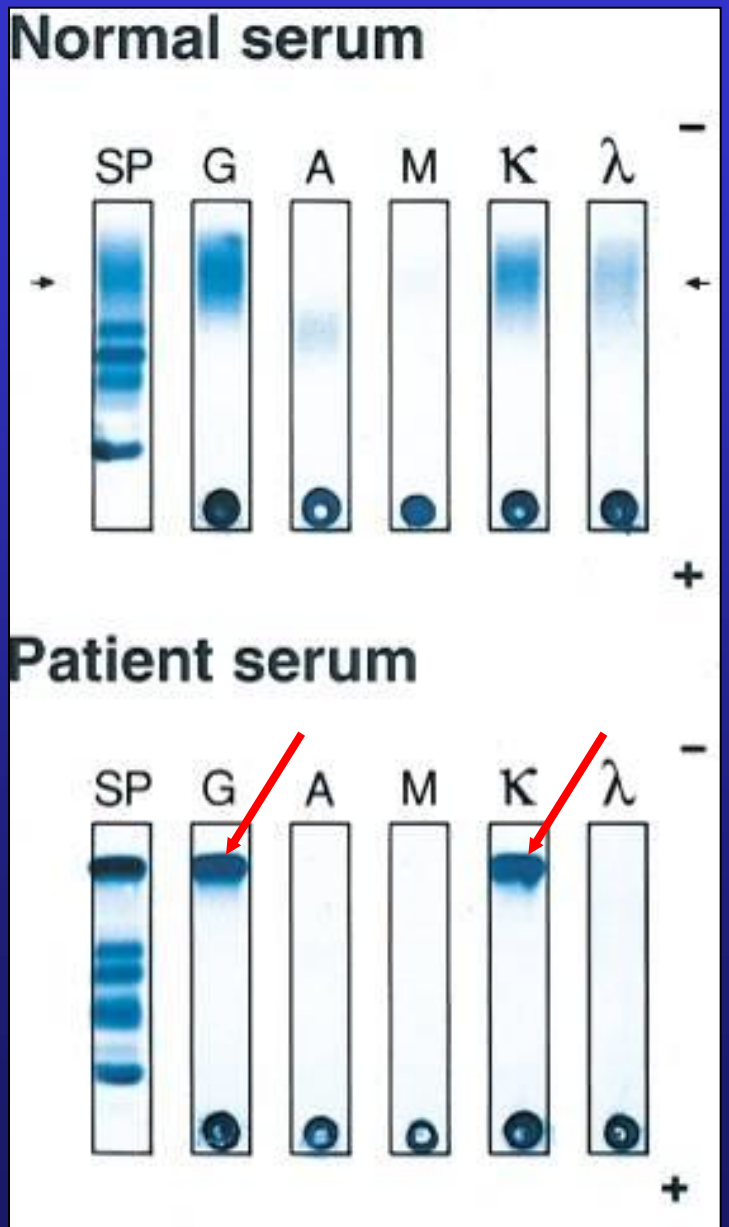
Clinical features

- Monoclonal IgG accounts for 50% and IgA for 20% of cases.
- A monoclonal light chain (Bence-Jones protein) is found in the serum of 15% of patients.
- IgD accounts for 2% of cases while bi-clonal gammopathies are found in 1% of cases.

Clinical features

- The serum M-protein is usually >30g/L of IgG and >25g/L of IgA.
- A Bence-Jones protein is found in the urine in 75% of patients.

Serum Protein Immunofixation



IgG-Kappa monoclonal gammopathy

Clinical variants

- Non-secretory myeloma:
  - Rare cases (1%) of plasma cell myeloma have plasma cells that synthesise but do not secrete Ig molecules, leading to absence of M-component.
  - Monoclonal cytoplasmic Ig is typically present in the neoplastic plasma cells when evaluated for immunophenotype.
  - Clinical features are the same, except for a lower incidence of renal insufficiency.

Clinical variants

- Non-secretory myeloma:
  - May have a lower level of plasmacytosis and less depression of normal Ig.
  - Due to the lack of serum or urine monoclonal Ig, diagnosis can be missed, unless BM biopsy with analysis of cytoplasmic Ig or other markers of plasma cells are performed.

Clinical Variant

- Smoldering (asymptomatic) myeloma:
  - These pts have higher levels of M-component and marrow plasmacytosis than pts with MGUS, and fulfil the minimal criteria for the diagnosis of plasma cell myeloma, but are asymptomatic and have no lytic bone lesions or other clinical features of myeloma including anemia, renal insufficiency, and hypercalcemia.

Clinical features

- Smoldering myeloma:
  - A small M-protein may be found in the urine and the concentration of normal serum Igs is often reduced.
  - In some pts, symptomatic plasma cell myeloma does not develop for years. These pts are typically not treated unless progression occurs.

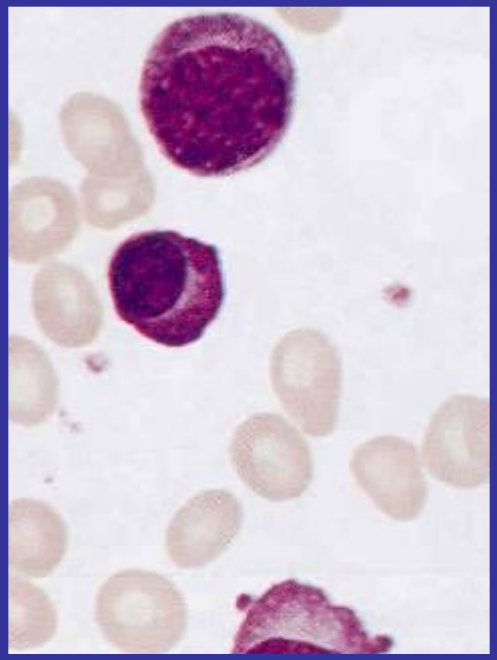
Clinical features

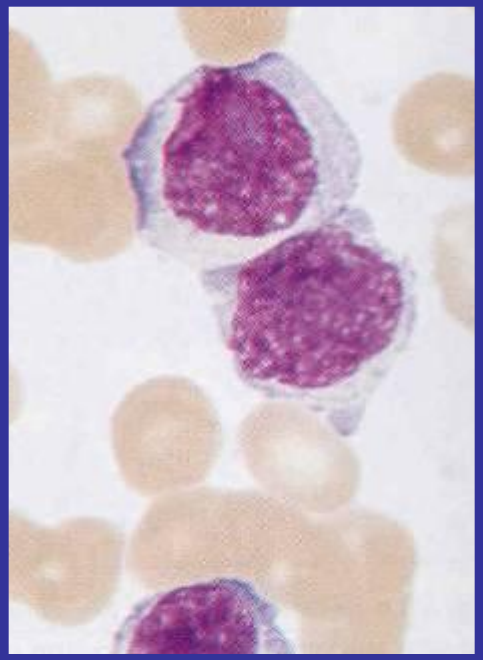
- Plasma cell leukemia (PCL):
  - PB involvement occurs rarely in plasma cell myeloma (2%) and is defined as circulating PB plasma cells (and plasmacytoid cells) $>2x10^3$/ml or 20% of PB leukocytes.
  - It may occur at the time of diagnosis (primary PCL) or evolve as a terminal complication during the course of a plasma cell myeloma (secondary PCL).

Clinical features

- Plasma cell leukemia (PCL):
  - More frequent in: light-chain only, IgE and IgD myeloma.
  - Less freqently seen in IgG or IgA myeloma.
  - Most clinical signs of myeloma are also seen in PCL, although osteolytic lesions and bone pain are less freq.
  - Lymphadenopathy and organomegaly are more freq.
  - Renal failure is common.
  - Aggressive disease with short survival.

Plasma cell leukemia





Plasma Cell Myeloma:Aetiology

- An increased risk (3-4 times) of myeloma has been described in cosmetologists, farmers, and laxative takers.
- Specific exposure agents include pesticides, petroleum products, high dose radiation in survivors of the atomic bomb at Hiroshima and Nagasaki (myeloma rate 4.7 times greater than controls).
- Low level radiation exposure is implicated in increased incidence of myeloma among radiologists and nuclear plant workers.

Aetiology

- Long-standing, chronic infections such as osteomyelitis or chronic antigenic stimulation such as rheumatoid arthritis has been considered a possible predisposing factor.
- A possible role for virus has been postulated with the finding of the HHV8 virus in myeloma marrow samples (not reproducible finding).
- The occurrence of myeloma in HIV-infected pts also suggests a possible aetiologic association.

Aetiology

- HIV-associated immunodepression may result in emergence of EBV-infected B-cell clones.
- Development of myeloma is postulated to follow the “two hit hypothesis”: initial antigenic stimulus giving rise to multiple benign clones with a second hit representing an “accident” or mutagenic event causing malignant transformation.

Aetiology

- While the initial antigenic stimulus can be established occasionally, in most cases the initial antigenic stimulus is unknown.
- Most myeloma proteins are autoantibodies that has been postulated to be directed against immunoregulatory autoantibodies.
- Although most myeloma proteins lack specificity for foreign antigen, there are rare documented cases of such specificity.

Precursor lesion:Monoclonal gammopathy of undetermined significance (MGUS)

- MGUS denotes de presence of a M-component in persons without evidence of plasma cell myeloma, WM, primary amyloidosis (AL), or other related disorders.
- It was considered to be benign and often called benign monoclonal gammopathy. However, a proportion of pts will evolve to myeloma or amyloidosis, so MGUS is considered more appropriate.

Precursor lesion:Monoclonal gammopathy of undetermined significance (MGUS)

- Pts are asymptomatic (no CRAB). The M-component is discovered unexpectedly during serum protein electrophoresis (typ < 30 g/L).
- Prevalence of MGUS is 1% in pats >50 y/o and 3% in those >70 y/o.
- About 75% of MGUS paraproteins are IgG; 15% IgM; 10% IgA.

Precursor lesion:Monoclonal gammopathy of undetermined significance (MGUS)

- Approximately 25% pts with MGUS develop plasma cell myeloma, primary amyloidosis, macroglobulinemia, or other lymphoproliferative diseases after follow-up for more than 20 yrs.
- The risk for malignant transformation is unrelated to the type of of M-protein.

Precursor lesion:Monoclonal gammopathy of undetermined significance (MGUS)

- The median interval from the recognition of the M-protein to diagnosis of myeloma, macroglobulinemia, or amyloidosis is aproximately 10 yrs.
- Thus, pts with MGUS must be followed indefinitely for evidence of progressive disease.

Precursor lesion:Monoclonal gammopathy of undetermined significance (MGUS)

- Plasma cells in MGUS resemble normal appearing mature plasma cells, without nucleoli. They constitute <10% of the nucleated cells in the BM.
- The plasma cells express monotypic cIg of the same isotype as the M-component in serum and urine.

Plasma Cell Myeloma:Macroscopy

- In plasma cell myeloma, the bone defects on gross examination are filled with a soft gelatinous, fish-flesh, hemorrhagic tissue.

Morphology

- BM biopsy:
  - Dx of myeloma is favored when a tumor mass of plasma cells is seen, displacing normal marrow elements.
  - The volume of marrow occupied can be estimated. In general, when 30% or more of the BM is involved, a Dx of plasma cell myeloma is likely.
  - In histologic sections the myeloma mass can be associated with a prominent osteoclastic activity.

Morphology

- BM aspiration:
  - Myeloma plasma cells vary from mature to immature, pleomorphic or anaplastic forms.
  - The mature plasma cells are usually oval, with a round eccentric nucleus with “spoke-wheel” or “clock-face” chromatin without nucleoli, with abundant basophilic cytoplasm and marked perinuclear hof.
  - Multinucleated, polylobated, pleomorphic plasma cells also occur.

Morphology

- BM aspiration:
  - Nuclear immaturity and pleomorphism (rarely occur in reactive plasma cells) are reliable indicators of neoplastic plasma cells.
  - Plasmablastic forms have dispersed nuclear chromatin, high N/C ratio, and prominent nucleoli. About 10% pts have plasmablastic morphology and this is associated with a poorer prognosis.

Morphology

- BM aspiration:
  - The cytoplasm of myeloma cells contains abundant ER, which may contain condensed or crystallized cytoplasmic Ig producing a variety of distinctive findings: multiple pale bluish-white or grape-like accumulation (Mott cells, Morula cells), cherry-red refractive round bodies (Russell bodies), vermillion staining glycogen-rich IgA (flame cells), overstuffed fibrils (Gaucher-like cells, thesaurocytes) and crystalline rods. However, these findings are not pathognomonic, can be found in reactive plasma cells.

Morphology

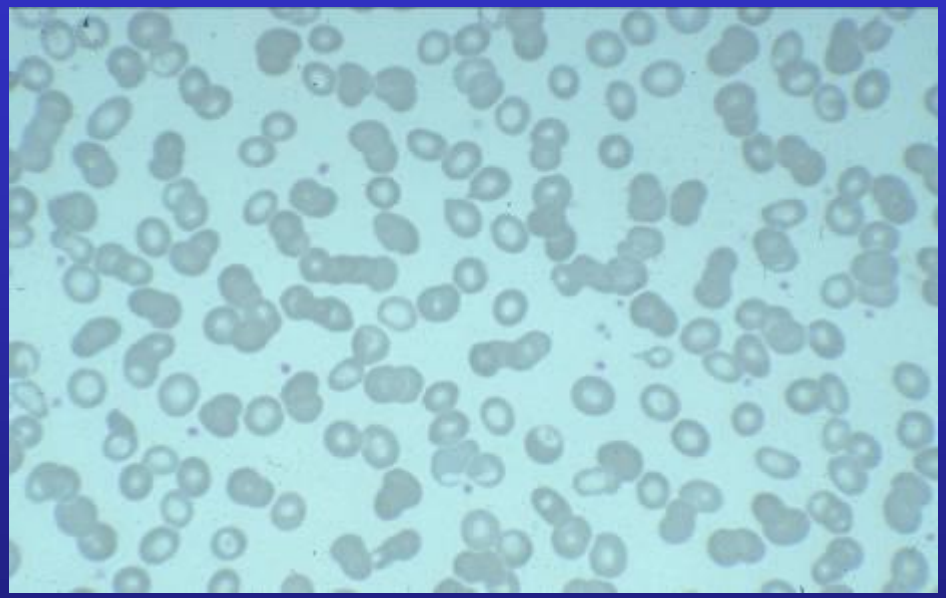
- Peripheral blood:

  Circulating plasma cells in plasma cell leukemia span a broad morphologic spectrum from mature to immature blastic forms not distinguishable from myeloblasts. Sometimes plasma cells have lymphoid-like morphology.

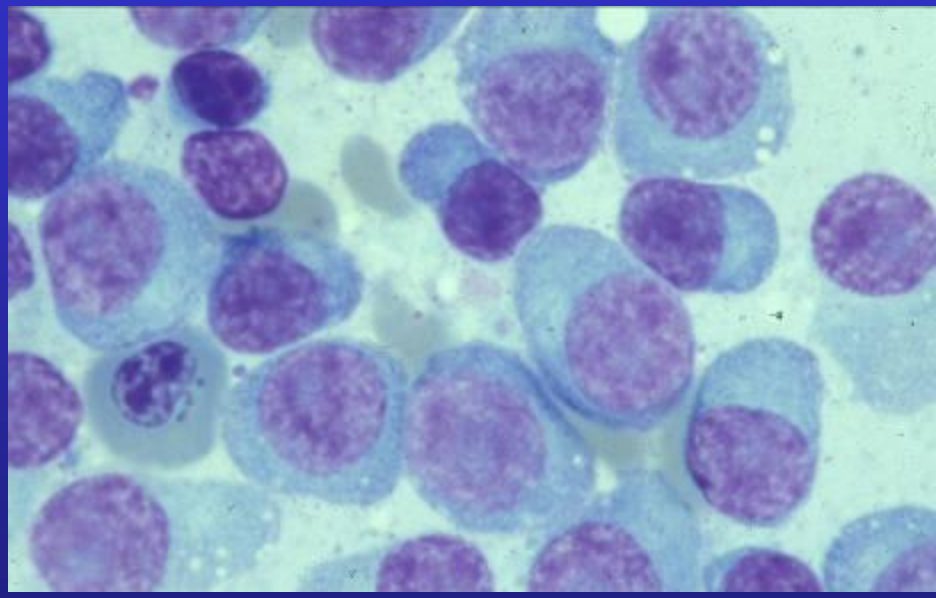
- Kidney:

  Bence-Jones protein accumulates as aggregates of eosinophilic material in the lumina of the renal tubules. Renal tubular reabsorption of Bence-Jones protein is largely responsible for renal damage in plasma cell myeloma.

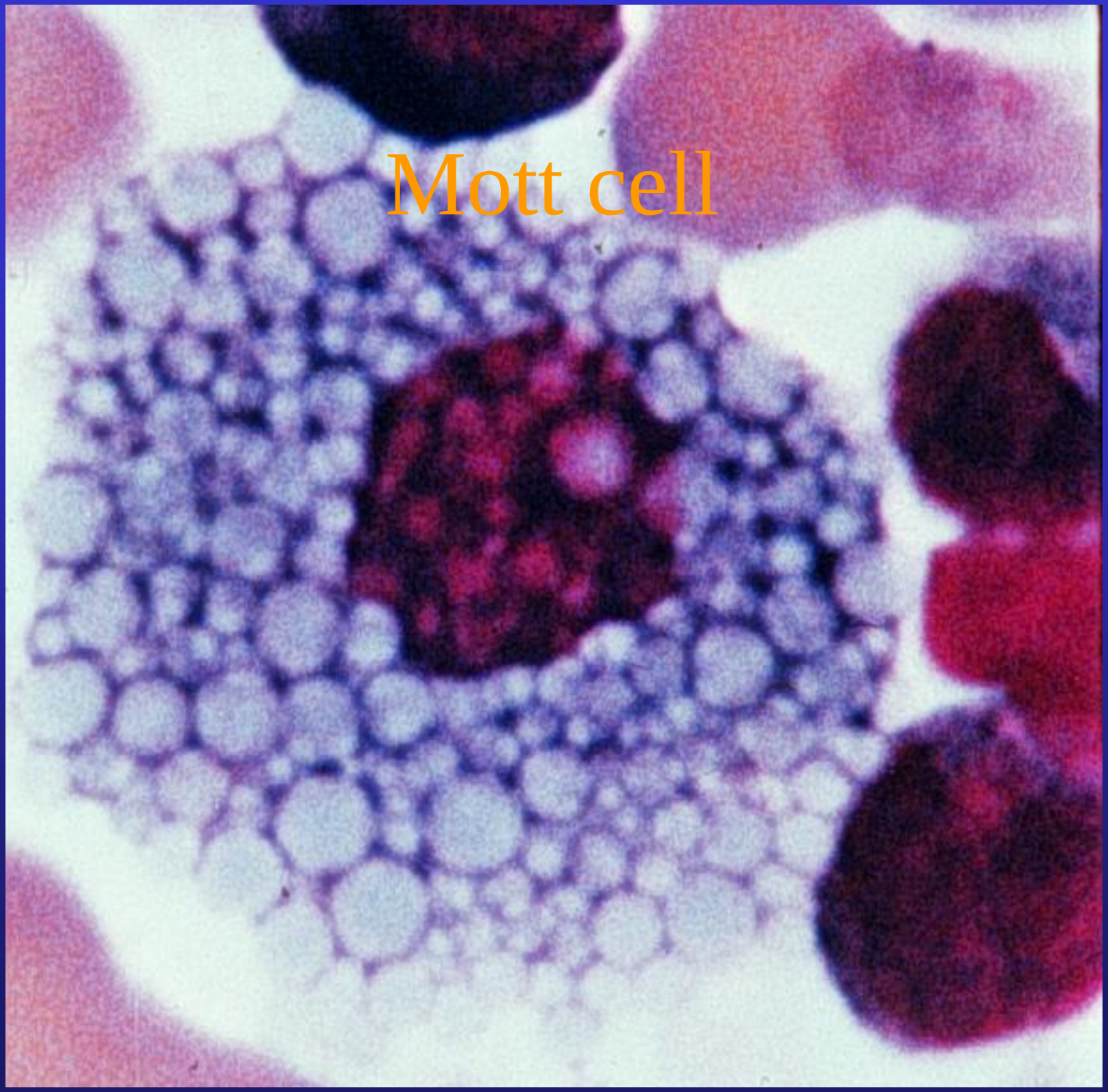
Multiple Myeloma



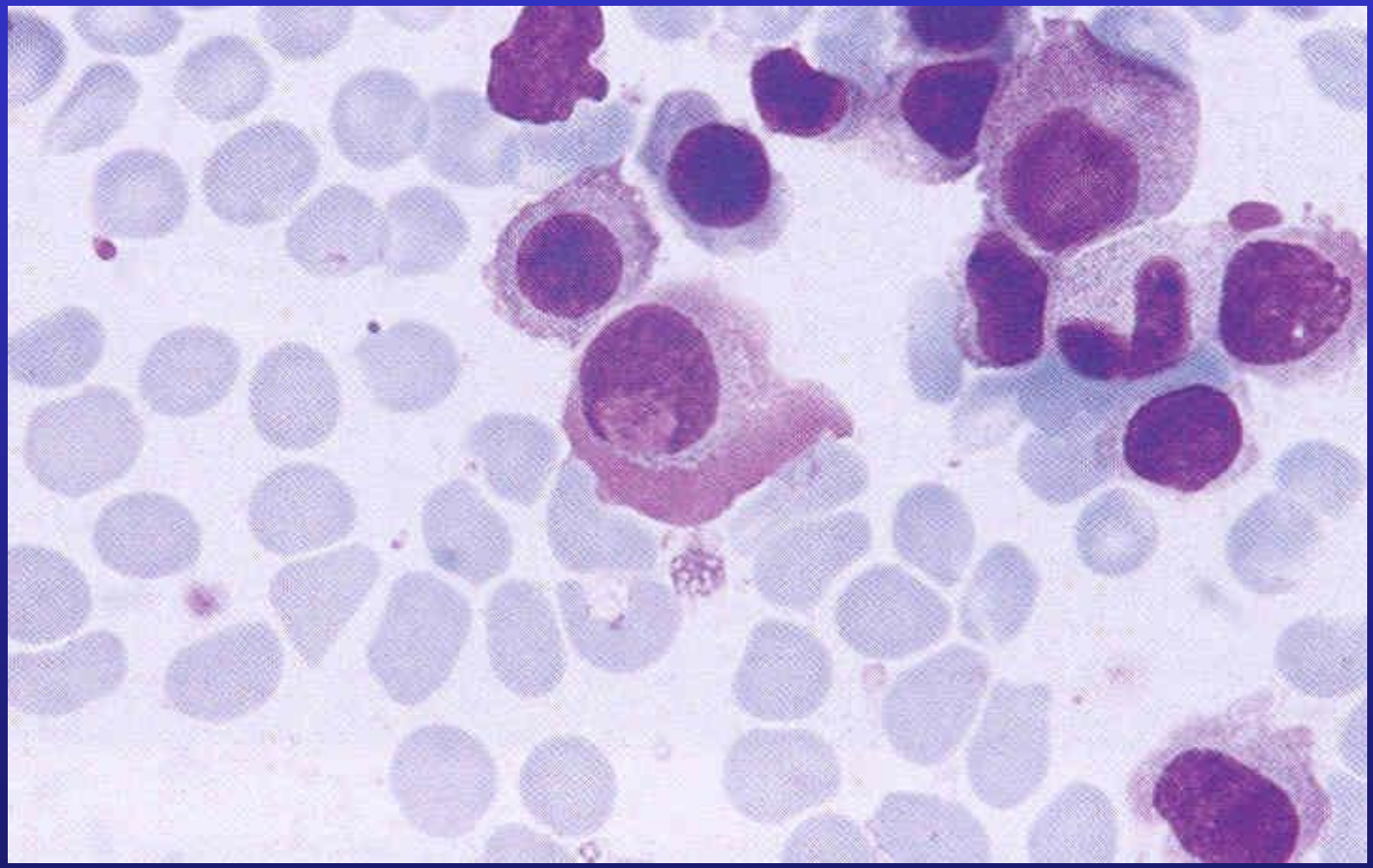
Peripheral blood: Rouleaux formation



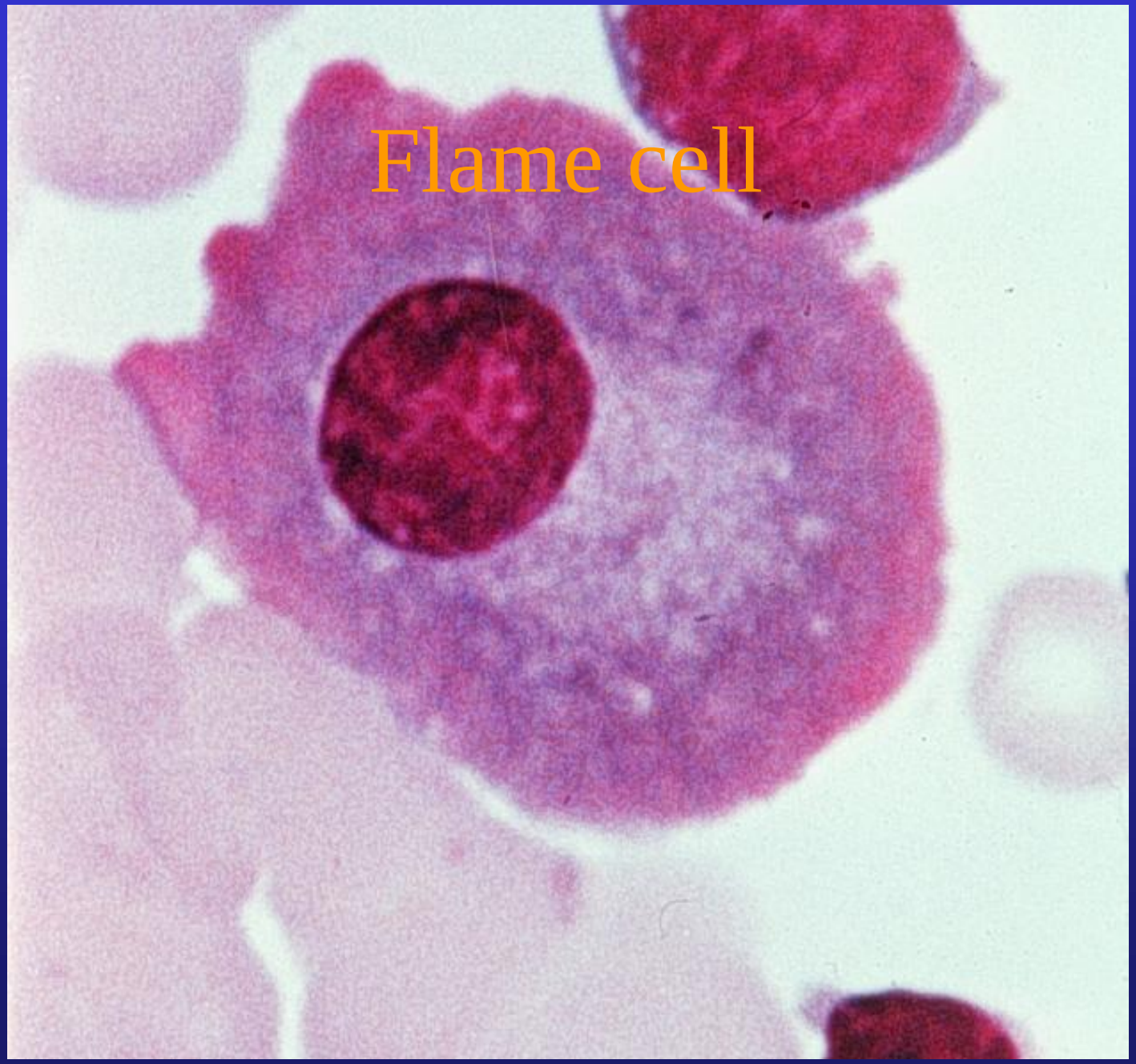
Bone marrow: plasma cell myeloma


Mott cell

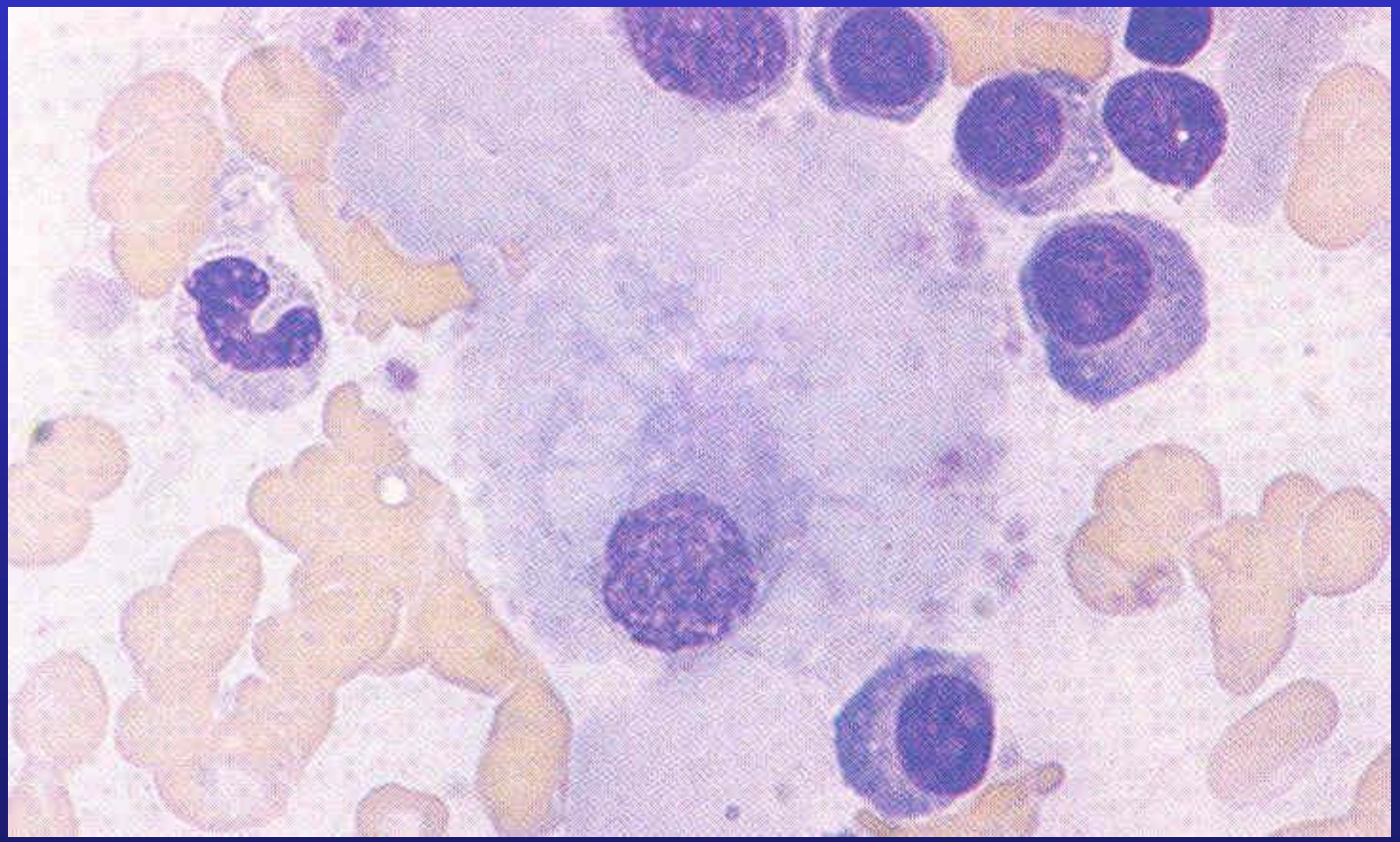
Dutcher bodies



Intranuclear inclusions


Flame cell

Thesaurocytes



E.R distended with Ig; voluminous ground glass cytoplasm

Immunophenotype

- Malignant plasma cells express monotypic cytoplasmic Ig and lack surface Ig. The Ig is most commonly IgG, occassionally IgA, and rarely IgD, IgE, or IgM. In 85% of cases, both heavy and light chains are produced; in 15% light chain only (Bence-Jones myeloma).
- Most but not all lack CD19 and CD20.
- CD38 and CD79a expressed in the majority of cases.

Immunophenotype

- In contrast with normal plasma cells that express CD19 and lack CD56/58, myeloma cells lack CD19 and express CD56/58.
- Collagen-1 binding proteoglycan syndecan-1 (CD138) is found in most cases of myeloma.
- VS38c is typically expressed.

Immunophenotype

- Circulating monoclonal idiotype-identical B lymphocytes have been reported.
- Occasional cases of myeloma and plasmacytoma may express CD10.
- The phenotype of plasma cell leukemia is comparable to that of myeloma, except for loss of adhesion molecules (CD56). Plasma cell leukemia is often of IgE or IgD, or expresses light chains only.
- Occasionally, myeloma may present with aberrant coexpression of myelomonocytic antigens.

Genetics

- Antigen receptor genes:
  - Clonal rearrangements are common.
  - While a single monoclonal Ig band is the rule in myeloma, multiple rearranged Ig bands are found in 5% of myeloma pts.
  - High frequency of Ig VH gene somatic mutation is consistent with derivation from a post-germinal centre, antigen-driven B-cell.

Genetics

- Antigen receptor genes:
  - Ig gene deletion is sometimes found.
  - In pts with light chain disease or Bence-Jones proteinuria, JH segments and/or parts or all of chromosome 14 may be lost.

Genetics

- Genetic abnormalities and oncogenes:
  - Cytogenetic analysis in most cases is hampered by the low proliferation fraction.
  - Cytokine-stimulated BM cultures and in-situ hybridization have increased the proportion of informative cases.
  - Structural and numerical chromosomal abnormalities are described in 20-60% of newly-diagnosed pts, with a mean of 30-40% and in 60-70% of pts with progressive disease, indicating an ascending scale of chromosomal aberration in pathogenesis.

Genetics

- Genetic abnormalities and oncogenes:
  - Complex karyotypes with multiple chromosomal gains and losses are the most frequent changes, but translocations, deletions and mutations are all reported.
  - Gains in chromosomes 3, 5, 7, 9, 11, 15, and 19; and losses in chromosomes 8, 13, 14, and X are the most common.
  - Among losses, monosomy or partial deletion of 13 (13q14) is the most common finding, occurring in 15-40% of newly-diagnosed cases.

Genetics

- Genetic abnormalities and oncogenes:
  - The most common structural abnormalities are with chromosomes 1 (15%), 11 (10%), and 14 (10%).
  - A t(11;14)(q13;q32), involving rearrangement of BCL1 locus, is the most common. This resuls in overexpression of CYCLIN D1.
  - Altered expression of the PAX-5 gene on chromosome 9 is thought to result in the loss of CD19, heralding the transition from normal CD19(+) plasma cells to CD19(-) myeloma cells.

Genetics

- Genetic abnormalities and oncogenes:
  - Deletion at 17p13 is associated with allelic loss of p53 is reported in 25% of the cases and may predict a poor outcome.
  - Deletion of the long arm of chromosome 7 has also been related to alteration of the multidrug resistance gene conferring an increased clinical drug resistant phenotype relevant to myeloma survival.

Genetics: Summary on Prognosis

- Unfavorable:
  -Hypoploidy
  -del 13, del 17p
  -t(4;14), t(14;16), t(14;20)
- Favorable:
  -Hyperploidy
  -t(11;14), t(6;14)

Postulated cell of origin

- Bone marrow-homing plasma cell

Prognosis and predictive factors

- Plasma cell myeloma is usually incurable, with a median survival of 3-4 years, and 10% survival at 10 years and more .
- Using the myeloma staging scheme, increased tumor burden and poor function are associated with shorter survival time.

Prognosis and predictive factors

- Myeloma staging scheme: estimation of the degree of marrow replacement by plasma cells in marrow core biopsies. Three stages have been defined:
    - Stage I <20%
    - Stage II 20-50%
    - Stage III >50% plasma cells

    Which predict progressively poorer prognosis.
- Pts in stage I have a median survival of > 60 months, stage II of 41 months, and stage III of 23 months.

Prognosis and predictive factors

- Myeloma pts with normal renal function experienced a 37-month median survival versus 8 months for those with renal insufficiency.
- Other prognostic factors include Hgb, calcium, lytic bone lesions, amount of the M component, and beta-2-microglobulin (B2M).

Prognosis and predictive factors

- Plasmablastic morphology is also associated with a poorer prognosis.
- The proliferation antigen Ki-67 also identifies pts with a poor prognosis (poor with >20%).
- Genetic abnormalities associated with a poorer prognosis (previous slide).

Plasmacytoma

Plasmacytoma: Subtypes

- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma

Plasmacytoma: Definition

- Clonal proliferation of plasma cells: cytologically, morphologically, and immunophenotypically identical to myeloma cells
- Localized growth pattern
  - Osseous: Solitary plasmacytoma of bone
  - Extraosseous: Extraosseous (extramedullary) plasmacytoma

Solitary Plasmacytoma of Bone

- Osseous plasmacytoma
- Localized bone tumor
- Solitary lytic lesion on X-rays
- No plasmacytosis in bone marrow away from lesion

Solitary Plasmacytoma of Bone

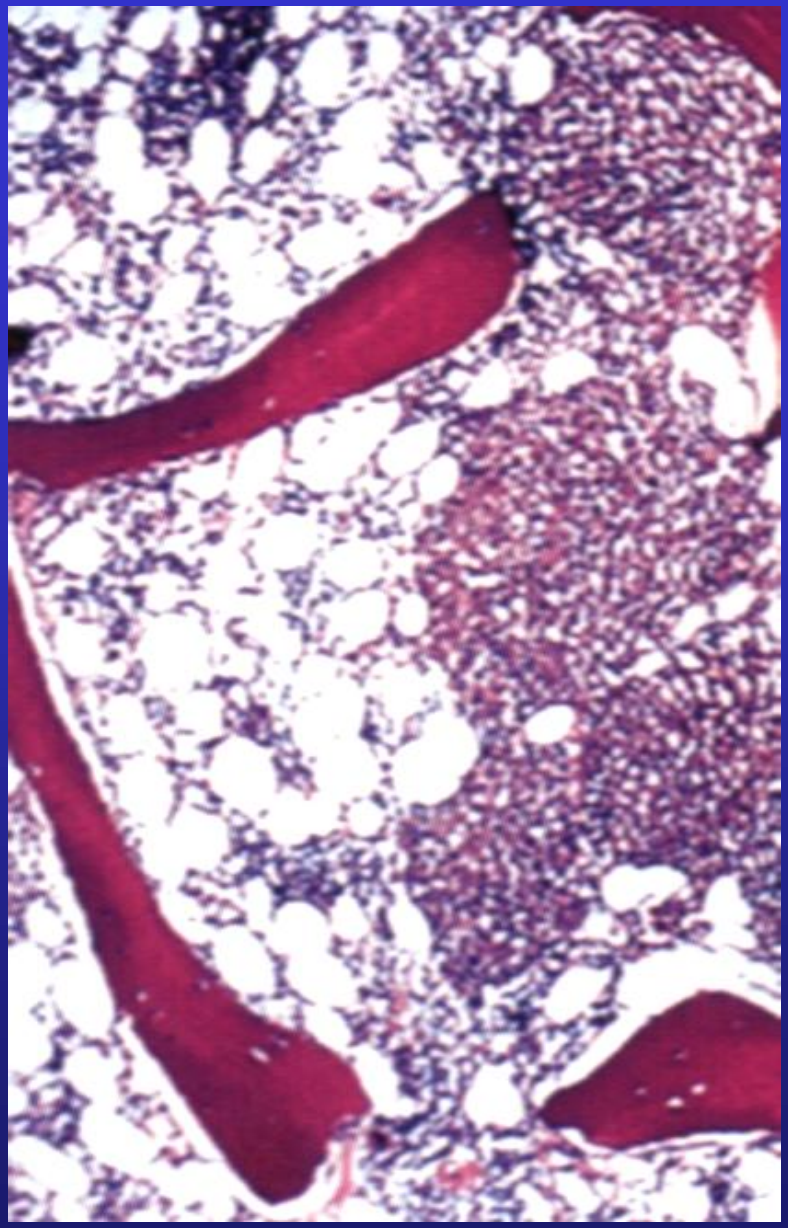
- Epidemiology
  - Rare (5% of plasma cell neoplasms)

Solitary Plasmacytoma of Bone

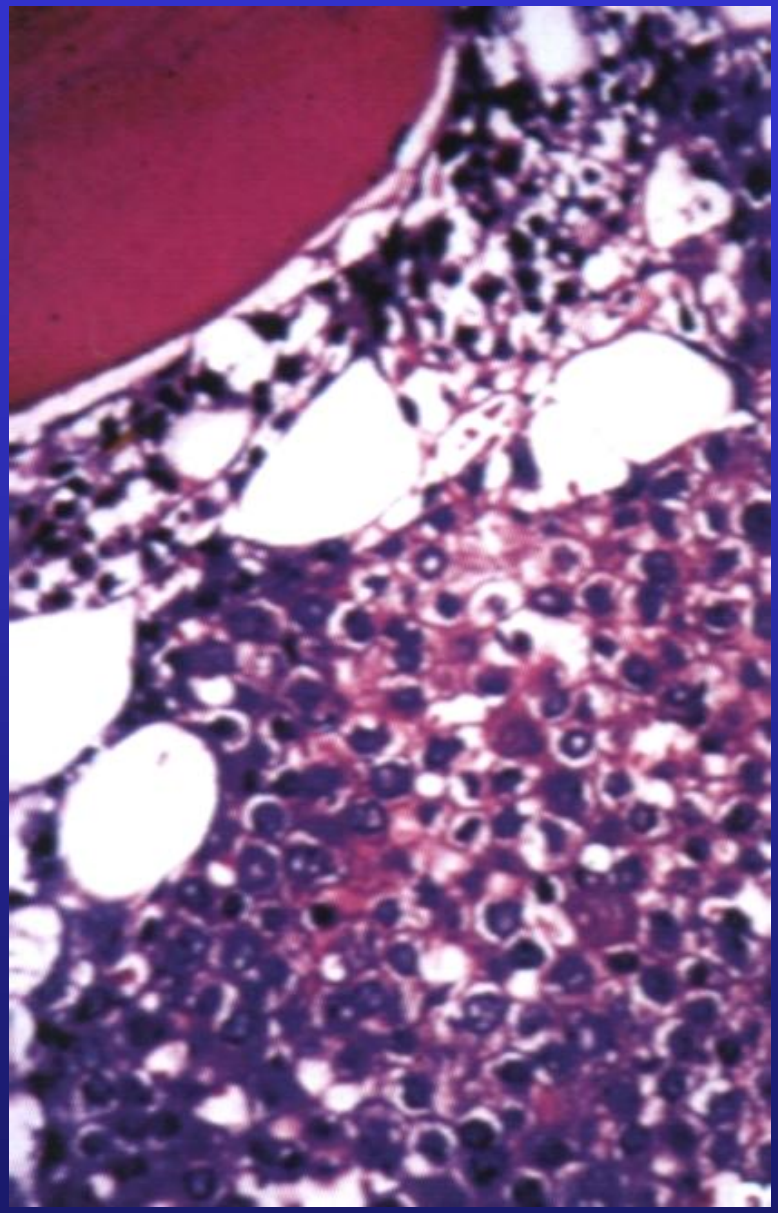
- Sites of involvement
  - Most commonly in marrow areas of most active hematopoiesis
    - Vertebrae
    - Ribs
    - Skull
    - Pelvis
    - Femur
    - Clavicle
    - Scapula

Solitary Plasmacytoma of Bone

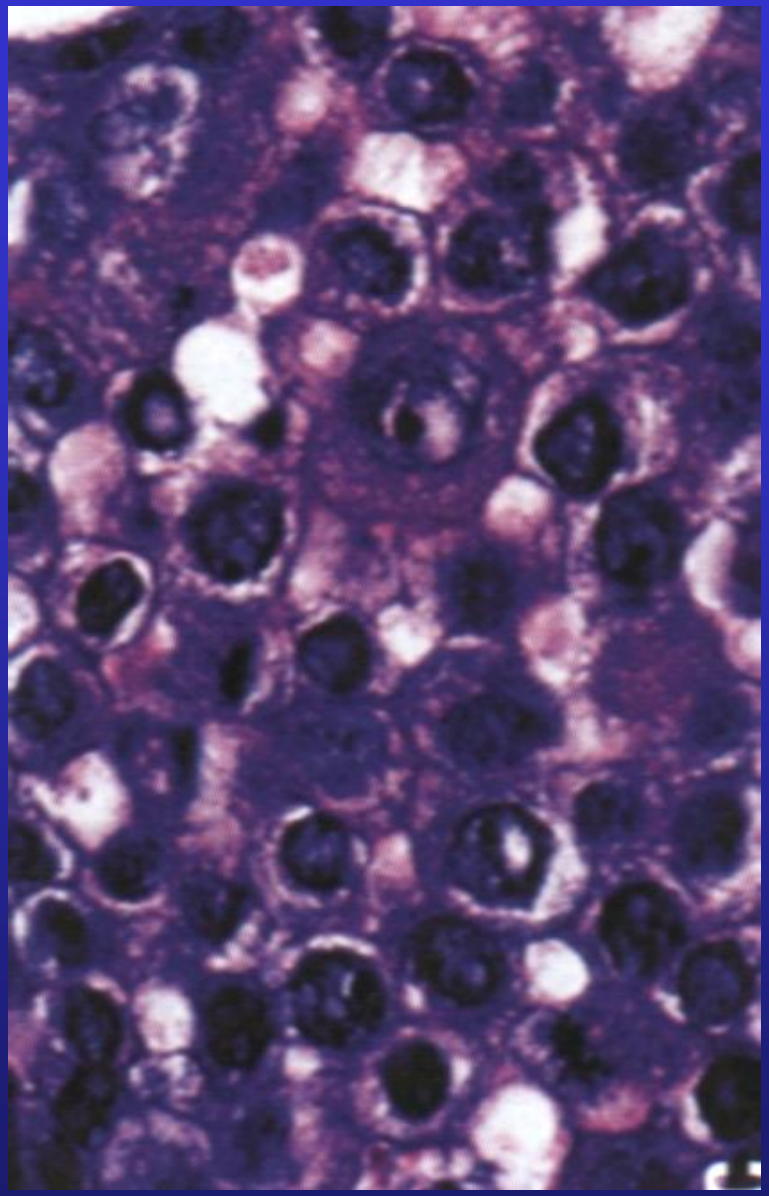
- Presentation
  - Bone pain, or
  - Pathological fracture
- No serum or urine M-protein (if present, it usually disappears after treatment)
- Morphology, immunophenotype, and genetics are identical to plasma cell myeloma



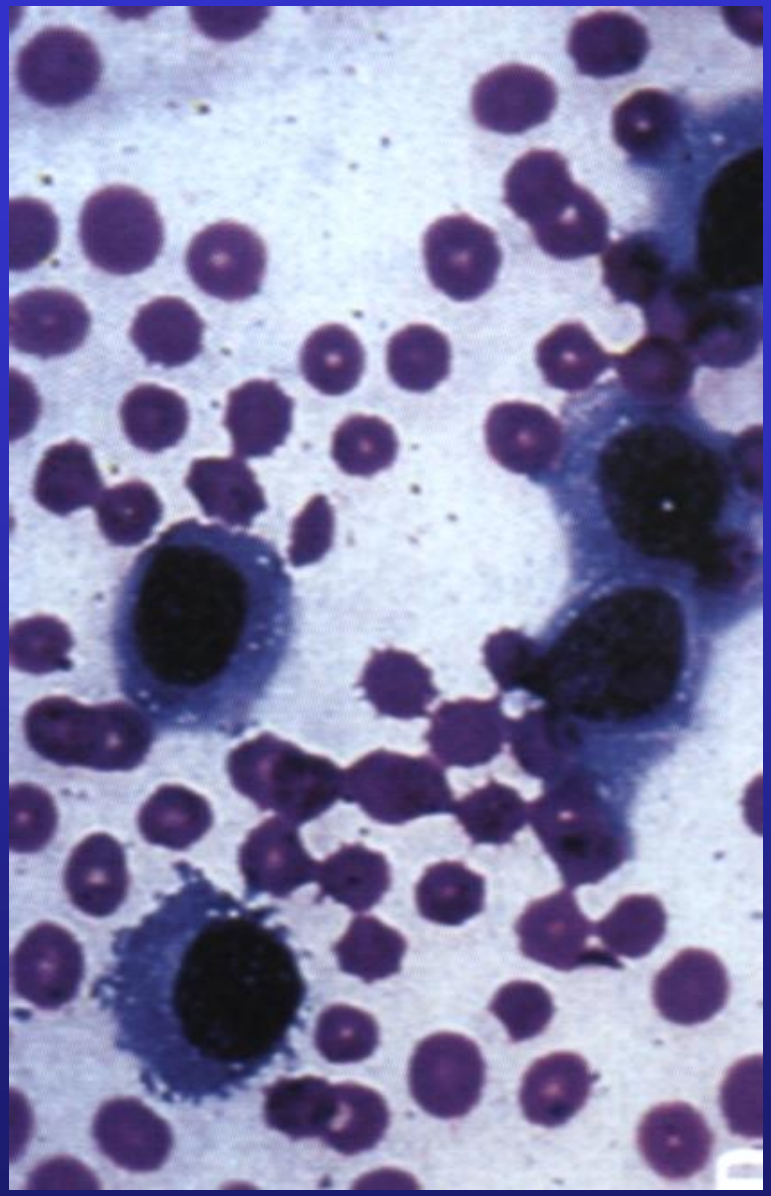
Solitary Plasmacytoma of Bone



Solitary Plasmacytoma of Bone



Solitary Plasmacytoma of Bone



Solitary Plasmacytoma of Bone

Solitary Plasmacytoma of Bone

- Treatment
  - Radiation therapy
- Prognosis at 10 years
  - 55% develop plasma cell myeloma
  - 35% cured
  - 10% local recurrence or develop another solitary lesion at different site

Extraosseous Plasmacytoma

- Extraosseous and extramedullary tumor

- Epidemiology
  - 3-5% of plasma cell neoplasms
  - Adults (median age 55)
  - Males : Female 2:1

Extraosseous Plasmacytoma

- Sites of involvement
  - Upper respiratory tract (80%)
    - Oropharynx
    - Nasopharynx
    - Sinuses
    - Larynx

Extraosseous Plasmacytoma

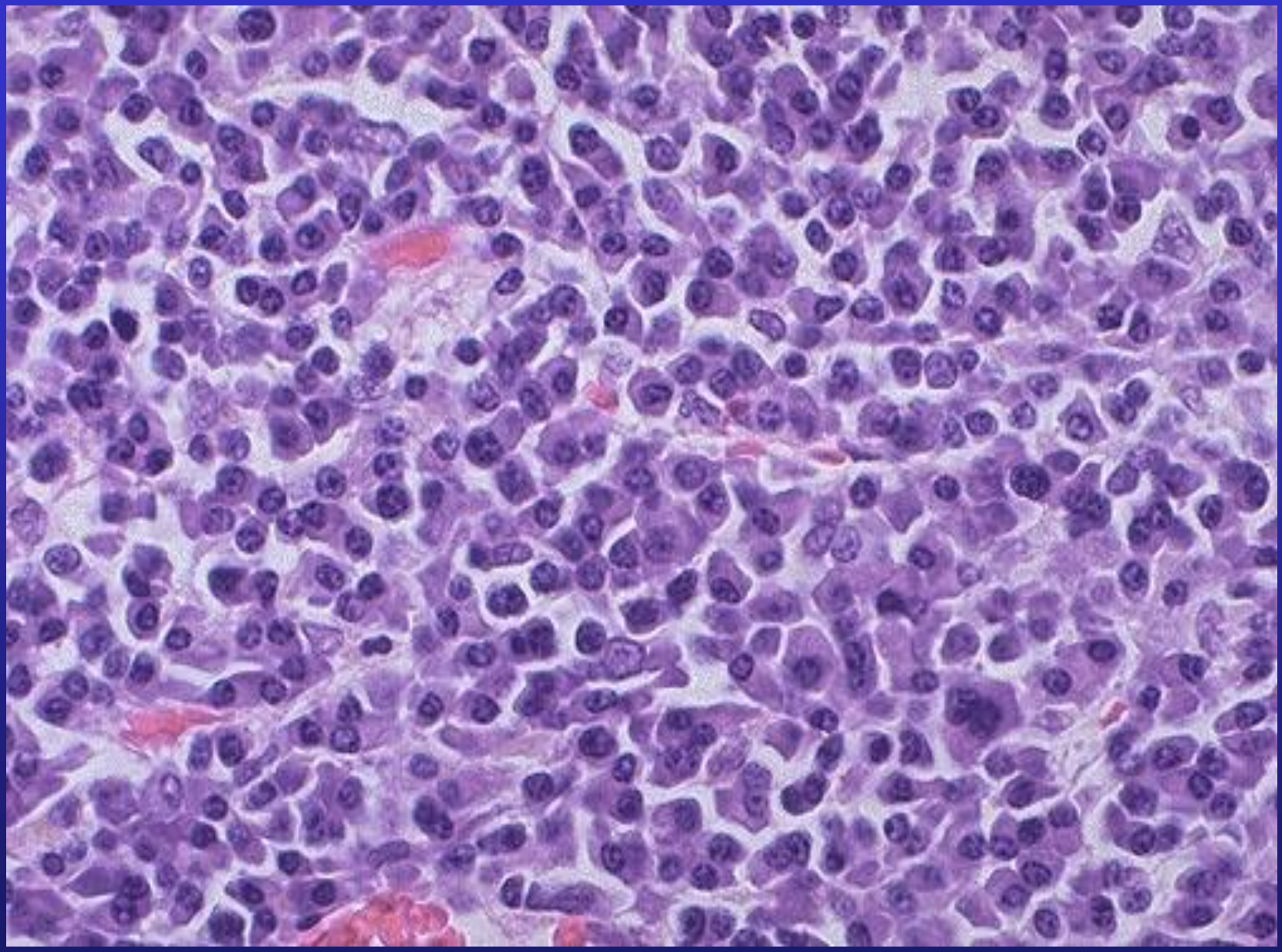
- Other sites of involvement
  - GI tract
  - Urinary bladder
  - Central Nervous System
  - Breast
  - Thyroid
  - Testis
  - Parotid gland
  - Lymph Nodes
  - Skin

Extraosseous Plasmacytoma

- Clinical features
  - No evidence of plasma cell myeloma
    - On bone marrow examination
    - By radiography
  - May have monoclonal gammopathy (15-20%)
  - No evidence of anemia, hypercalcemia, or renal insufficiency

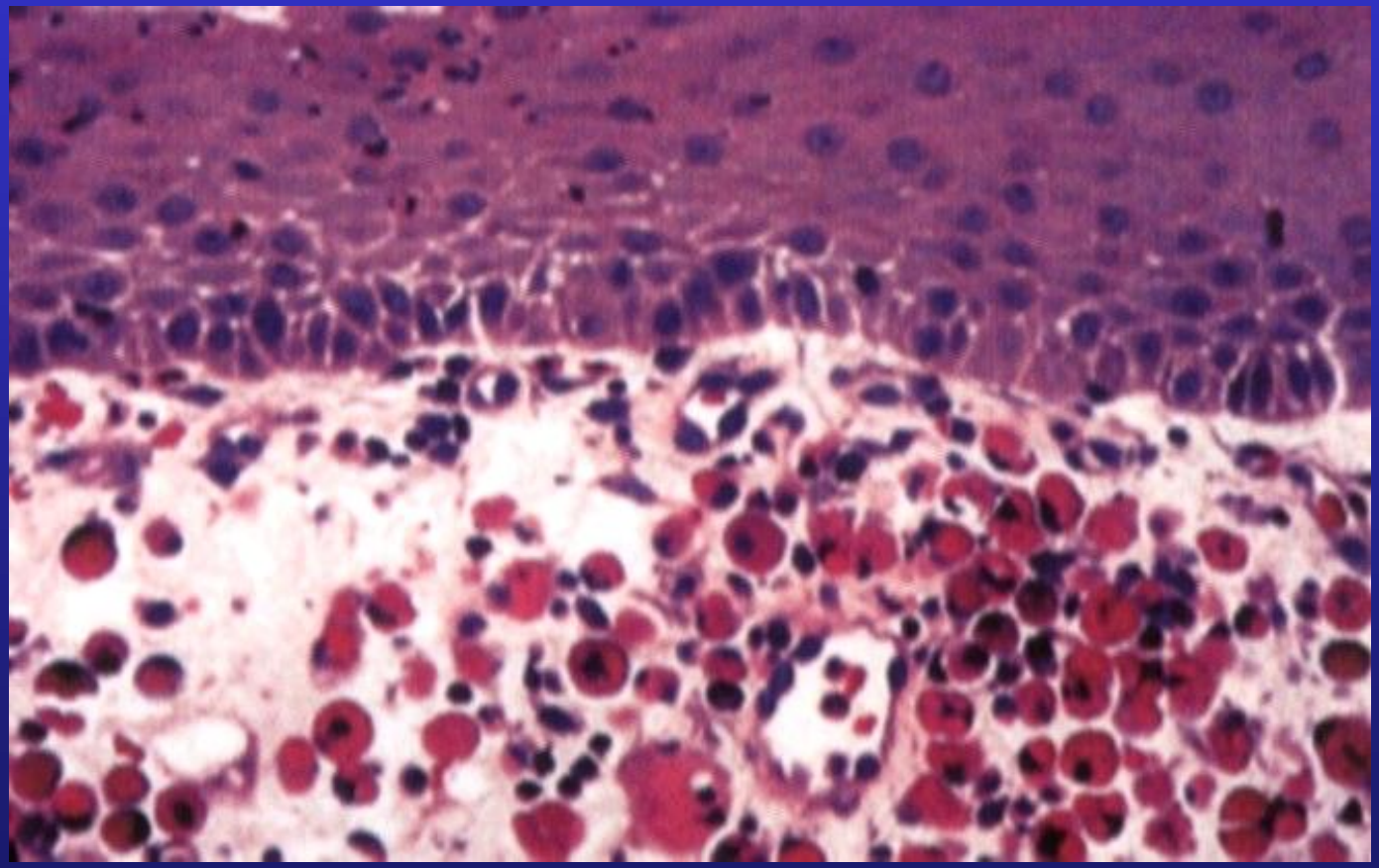
Extraosseous Plasmacytoma

- Morphology
  - Similar to osseous plasmacytoma
  - Need to exclude MALT lymphoma with marked plasmacytic differentiation

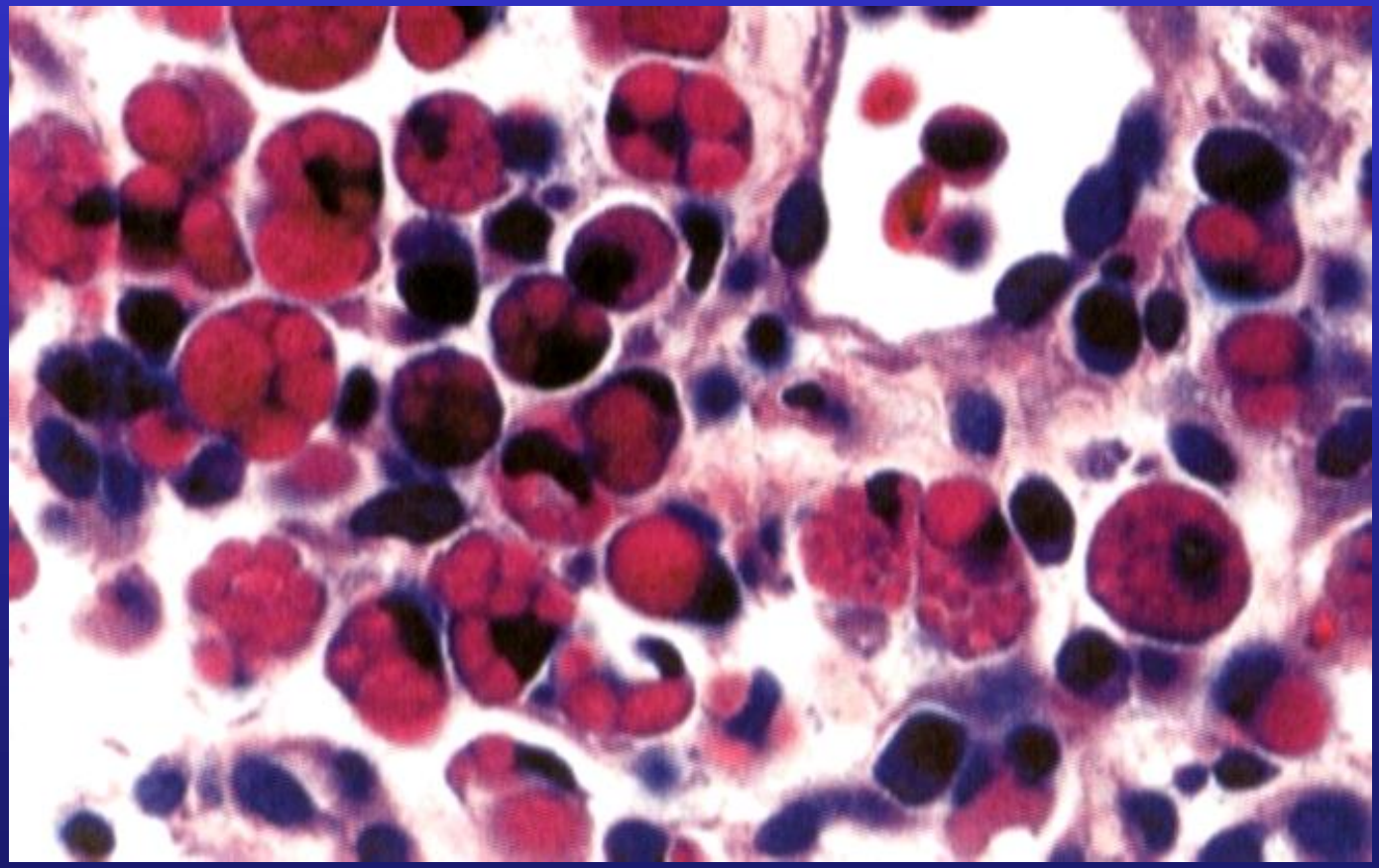


Extraosseous Plasmacytoma

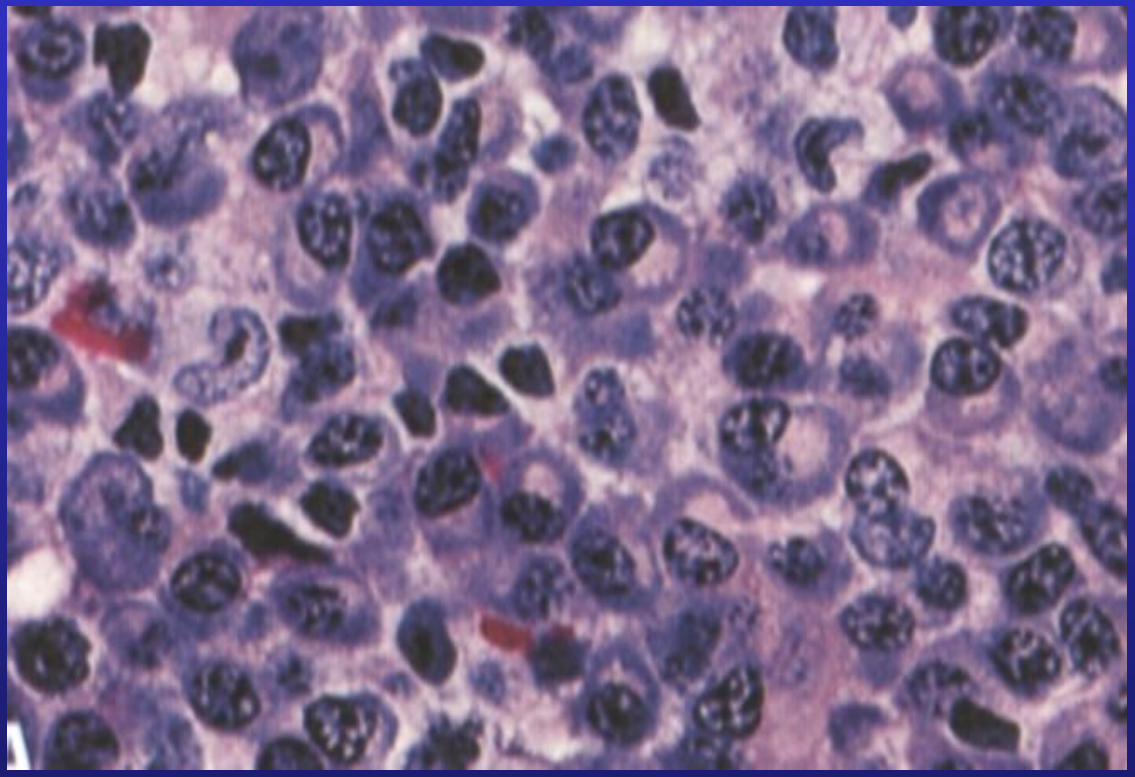
Extraosseous Plasmacytoma



Extraosseous Plasmacytoma

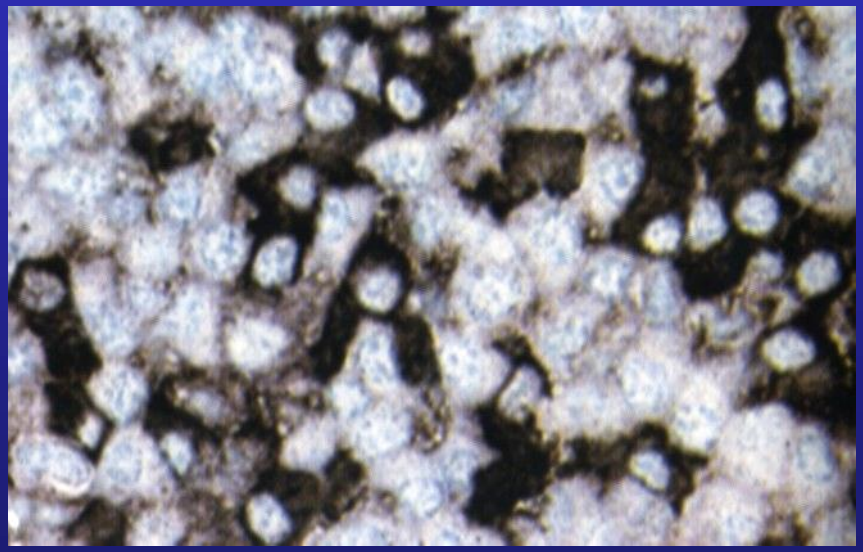


Differential Diagnosis: reactive plasma cell infiltrates

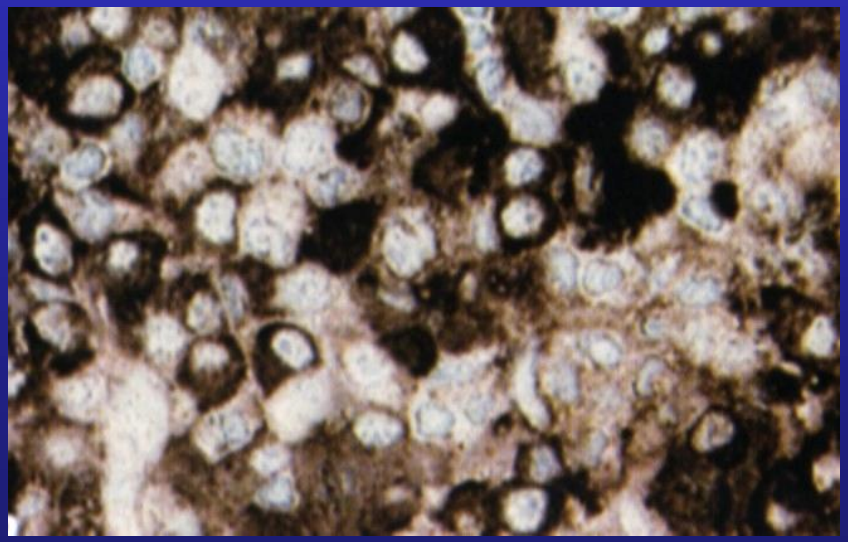


Differential Diagnosis: reactive plasma cell infiltrates

- Polyclonal kappa and lambda light chain expression



lambda



kappa

Extraosseous Plasmacytoma

- Immunophenotype and genetic features
  - Not extensively studied
  - Appear to be identical to those of plasma cell myeloma

Extraosseous Plasmacytoma

- Treatment
  - Radiation therapy
- Prognosis
  - 25% regional recurrences
  - 15% develop plasma cell myeloma