University of Baghdad
College of Medicine
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Title: WBC Disorders – Part 2B

Grade: 4

Module: PATHOLOGY (Hematology)

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WBC Disorders (Part 2B): Plasma Cell Disorders

https://www.youtube.com/watch?v=jdytgW5wKa4

Learning Objectives:

By the end of this session the student should be able to:

1. Clarify the pathogenesis of multiple myeloma (MM).
2. Describe the pathological features of MM.
3. Diagnose and investigate MM.
4. Differentiate between the diagnosis of MM and monoclonal gammopathy of undetermined significance (MGUS).
5. Predict the prognosis of MM and MGUS.

PLASMA CELL NEOPLASMS

PCNs originate from a neoplastic clone of B-lymphoid cells that differentiates into plasma cells and ***secrete*** *a*

single complete and/or partial immunoglobulin (Ig)

These disorders are also called monoclonal gammopathies , due to the presence of usually *excessive amounts of serum Ig*, referred to as an *M-protein* or *paraprotein*.

The plasma cell dyscrasias can be divided into many variants:

1. Multiple myeloma

MM is the most common of malignant plasma cell dyscrasias.

Pathogenesis:

- Dysregulation or increased expression of cyclin D1 & D3.
- IL-6 is a potent growth factor for myeloma cells and is often active by an autocrine mechanism.

Pathogenesis

Hyperploidy is present in about half of the tumors.

Non-hyperploid cases have a high incidence of *translocations* involving the Ig heavy-chain gene (IGH) on chromosome 14

Monoallelic loss of 13q is frequent in both categories.

All these genetic abnormalities are *also seen in MGUS*

The common M-components:

- **IgG kappa** (60%)
- **IgA** (20- 25%)
- **κ or λ light chains** (15-20%)

Because of their low molecular weight, the *free light chains* are rapidly excreted in the urine, where they are termed:

Bence-Jones proteins (BJP)

Even more commonly, malignant plasma cells produce both serum M components & BJP in urine.

Gross pathologic features:

Multifocal destructive bone lesions:

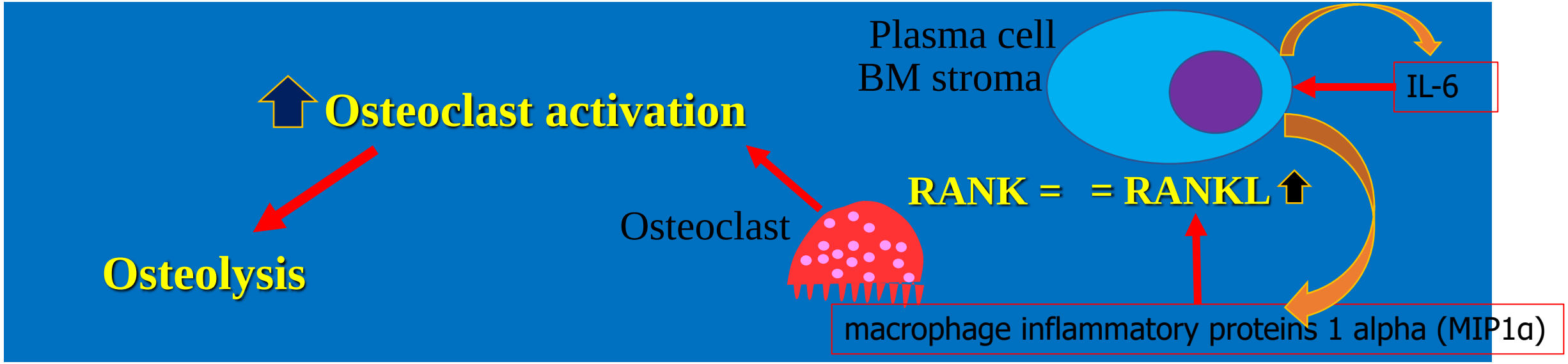
- Vertebral column (65%)
- Ribs (45%)
- Skull (40%)
- Pelvis (30%)
- Femur (25%)

Pathological fractures

Vertebral collapse

The most common site of bone lesion in multiple myeloma is:

A. Humerus
B. Pelvis
C. Vertebral column
D. Skull
E. Ribs



The osteolytic lesions are caused by osteoclast activation resulting from high serum level of RANKL, produced by plasma cells and BM stroma, which binds to RANK receptors on the osteoclast surface, which promotes the differentiation and activation of osteoclasts.

These focal lesions generally *begin in the medullary cavity*, erode the cancellous bone, and *progressively destroy the cortical bone*.

Microscopic features:

BM: Clonal plasma cells constitutes ≥ 10% of ANCs.

Morphologically:

- resemble normal mature plasma cells,
- more often show prominent nucleoli or abnormal cytoplasmic inclusions containing Ig.

Infiltrations of soft tissues (plasmacytomas)

Leukemic picture may emerge (plasma cell leukemia).

Metastatic calcification (hypercalcemia).

Myeloma nephrosis:

A. Proteinaceous casts (BJPs); prominent in the distal convoluted tubules & collecting ducts.
B. Amyloid.
C. Multinucleate giant cells.
D. The epithelial cells lining the cast-filled tubules become necrotic or atrophic.
E. Pyelonephritis.
F. Interstitial infiltrates of plasma cells are seen.

The clinical manifestations result from :

A. The destructive effect of the infiltrating neoplastic cells in various tissues.

B. The abnormal immunoglobulins secreted by the tumors.

1. *Bone pain*
2. *Features of Anemia*
3. *Recurrent bacterial infections*
4. *Features of renal failure and/or hypercalcemia*
5. *Bleeding tendency*
6. *Amyloidosis*
7. *Hyperviscosity syndrome*

Diagnosis of multiple myeloma:

Both criteria must be met:

1. **Clonal BM plasma cells ≥10% or plasmacytoma on biopsy**
2. **Any one or more of the following:**
   - Evidence of **end organ damage (CRAB):**
     - Hyper**C**alcemia
     - Renal insufficiency
     - Anemia: Hb <10 g/dL
     - Bone lesions
   - **Clonal BM plasma cell percentage ≥ 60%**
   - **Involved free light chain level** must be 100 mg/L
   - **> 1 focal lesions on MRI (at least 5 mm in size)**

The characteristic clonal plasma cell immunophenotype is:

$CD38^{high}$, $CD138^{high}$

$CD45^{low}$, $CD19^{low}$

CD56 +

Which of the following combination of markers is consistent with clonal plasma cells?

A. $CD38^{high}$, $CD138^{high}$, $CD45^{low}$, $CD19^{low}$, $CD56^{+}$
B. $CD38^{high}$, $CD138^{low}$, $CD45^{low}$, $CD19^{high}$, $CD56^{+}$
C. $CD38^{high}$, $CD138^{high}$, $CD45^{high}$, $CD19^{low}$, CD56-
D. $CD38^{high}$, $CD138^{high}$, $CD45^{low}$, $CD19^{high}$, $CD56^{-}$

Investigations of MM

- **Electrophoresis** is an important diagnostic tool.

  In 97% of cases a monoclonal spike of complete Ig or Ig light chain can be detected in the serum and/or urine.

- **CBP**:

  Anemia is usually normochromic normocytic or macrocytic.

  Rouleaux formation is marked.

  Neutropenia & thrombocytopenia (in advanced disease).

  Few plasma cells appear in the blood film in 15% of cases.

- High ESR.

- **BM**: increased plasma cells.

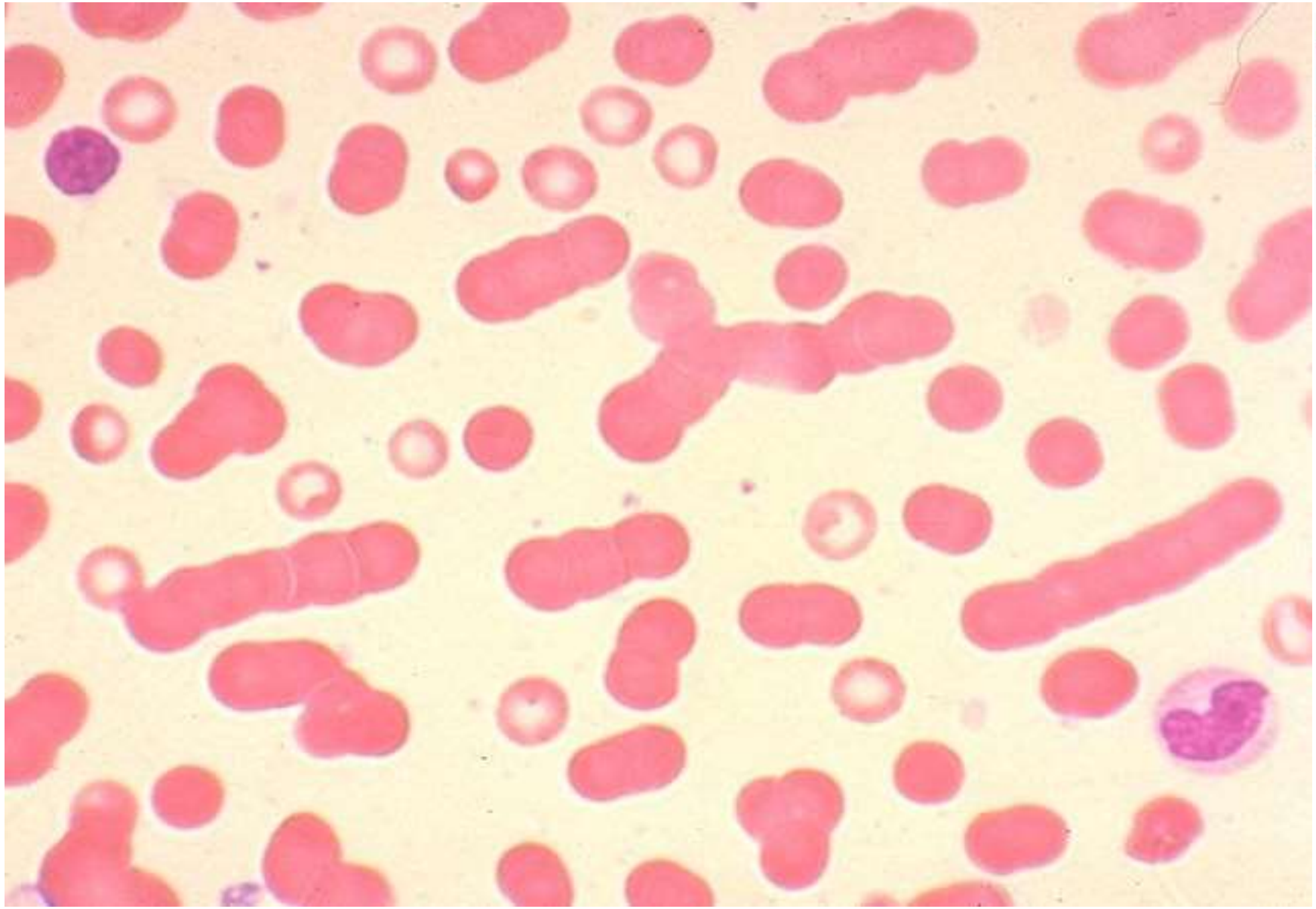
❑ Radiological

the diagnosis is strongly suspected when the characteristic focal ***osteolytic punched-out lesions*** are present (in 60% of cases) especially when located in the vertebrae or calvarium.

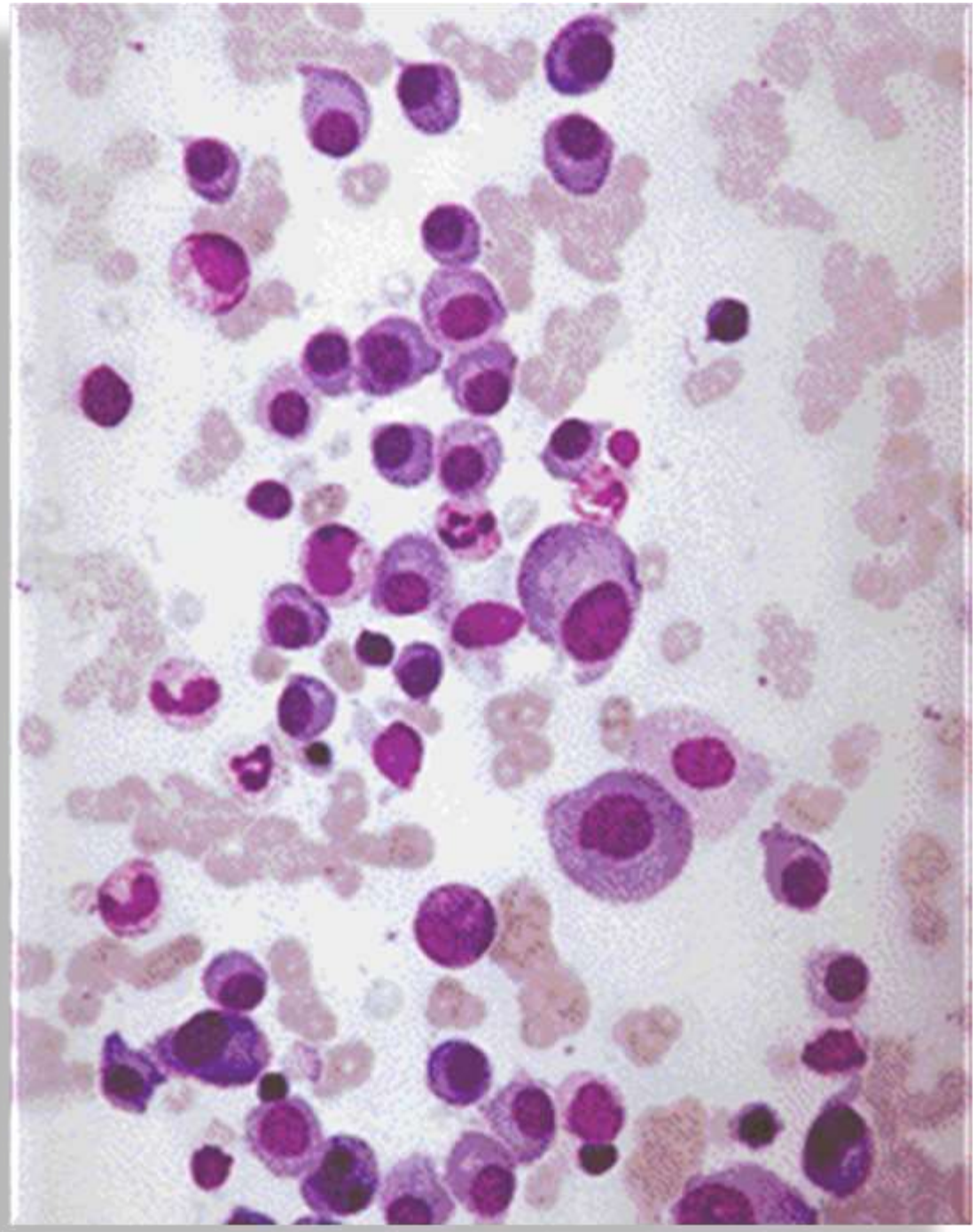
Generalized osteoporosis (20%)

No bone lesions (20%)

In addition, ***pathological fractures*** or ***vertebral collapse*** are common.

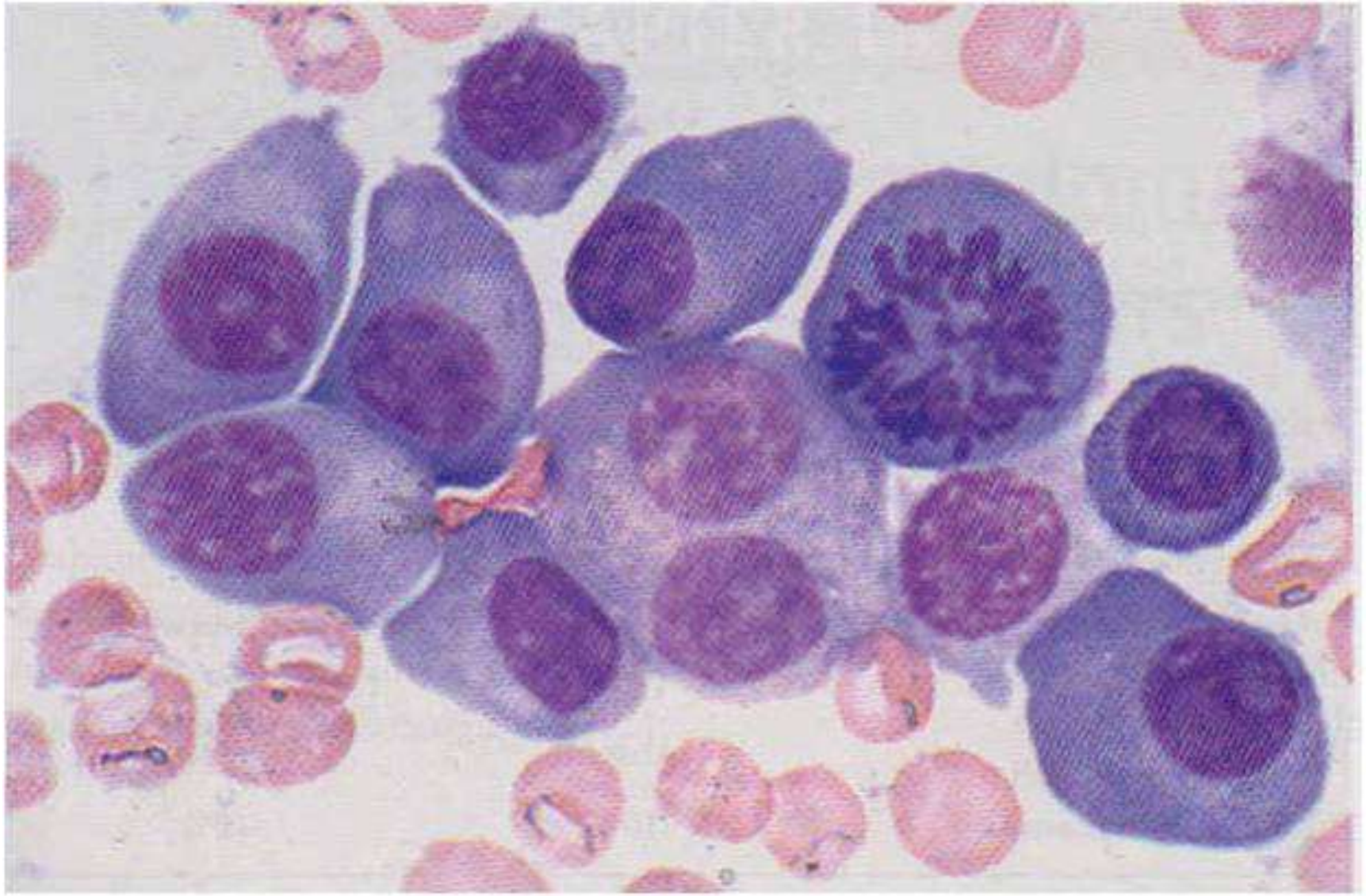


Blood film, showing marked rouleaux formation

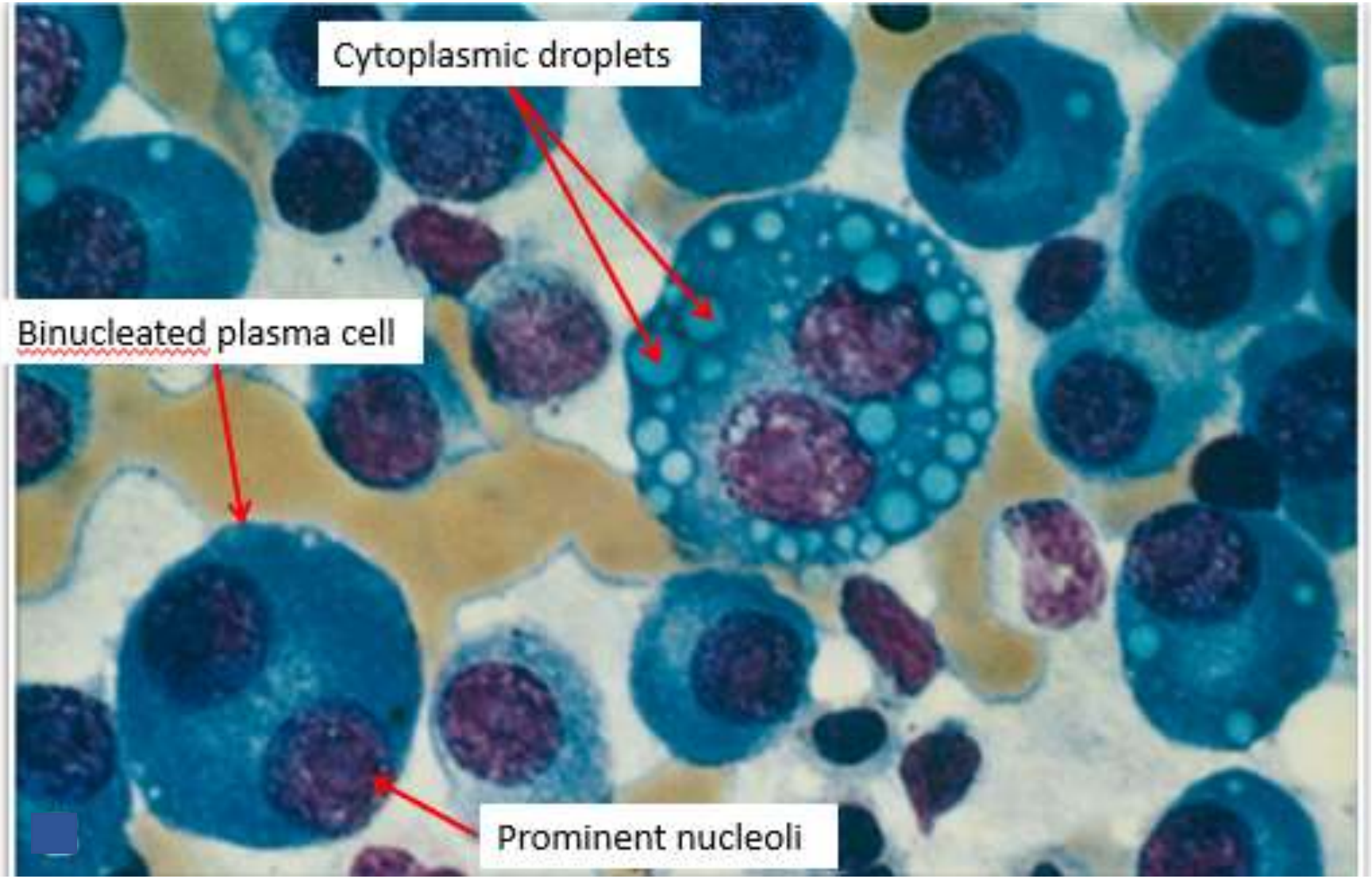


Describe the changes in the BM smear?

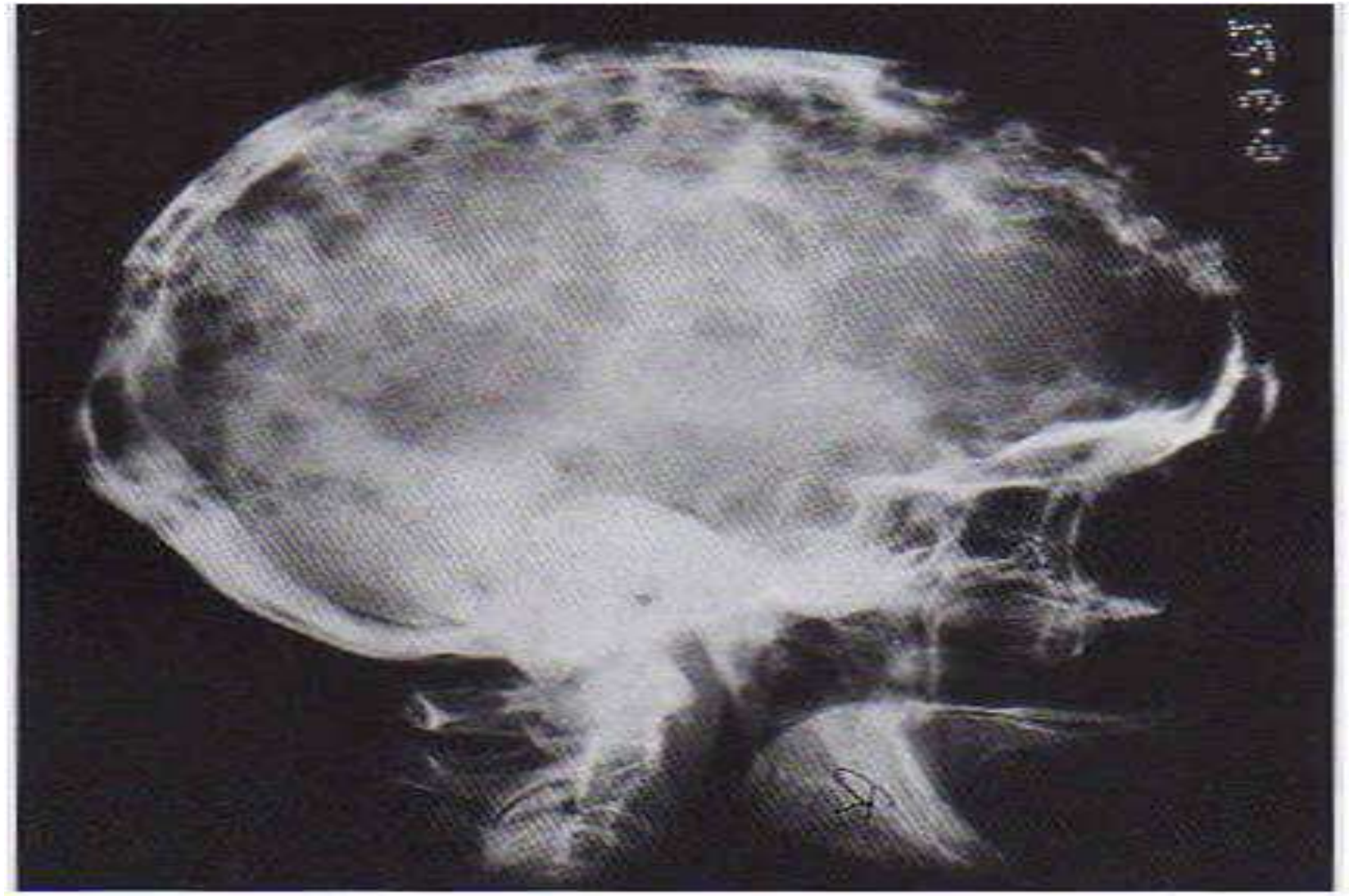
Bone marrow, MM, showing extensive infiltration by plasma cells



BM, MM, showing Increased number of plasma cells



BM aspirate, Multiple myeloma, showing normal marrow cells are largely replaced by plasma cells, including atypical binucleated forms, prominent nucleoli, and cytoplasmic droplets containing immunoglobulin.



Skull X-ray: Osteolytic punched-out lesions are most obvious in the calvarium.

Further investigations include:

- Serum Calcium increased in 45% of patients.
- Typically, the serum alkaline phosphatase is normal (except following pathological fractures).
- S. Creatinine is raised in 20% of cases.
- S. Albumin decreases with advanced disease.
- S. β_2-microglobulin is often raised (levels < 4 mg/L imply a relatively good prognosis).
- High CRP.

Prognosis:

Multiple myeloma is a progressive disease.

Patients with serum **β_2-microglobulin > 5.5 mg/L** and serum **albumin level < 35 g/L** have **poor** survival as do those with **frequent circulating plasma cells**.

2. Monoclonal Gammopathy of Undetermined Significance (MGUS)

A ***serum paraprotein*** may be sometimes be detected in ***asymptomatic individuals*** without any evidence of MM or other underlying disease and is termed MGUS.

For the Diagnosis of MGUS all 3 criteria must be met:

1. Serum monoclonal protein (non-IgM type) < 3 g/dL.
2. Clonal BM plasma cells < 10%.
3. Absence of end-organ damage.

There are **no** bone lesions, **no** BJP in urine.

MGUS has a high prevalence (3.2% and 5.8% in individuals over 50 and 70 years of age, respectively), making this the most common plasma cell dyscrasia.

Patients with MGUS develop a well-defined plasma cell neoplasm (myeloma, lymphoplasmacytic lymphoma, or amyloidosis) at a rate of 1% per year.

The diagnosis of MGUS should be made with caution and only after careful exclusion of all other forms of monoclonal gammopathies, particularly MM.

3. Localized Plasmacytomas (solitary plasmacytoma)

These are **isolated plasma cell tumors** involving the

skeleton or the ***soft tissues***

Solitary Skeletal Plasmacytomas; most of these develop full-blown multiple myeloma over a period of 5 - 10 years.

Extraosseous lesions occur mainly in mucosa of the upper respiratory tract, GIT or the skin

4. Plasma cell leukemia

PCL occurs either as a:

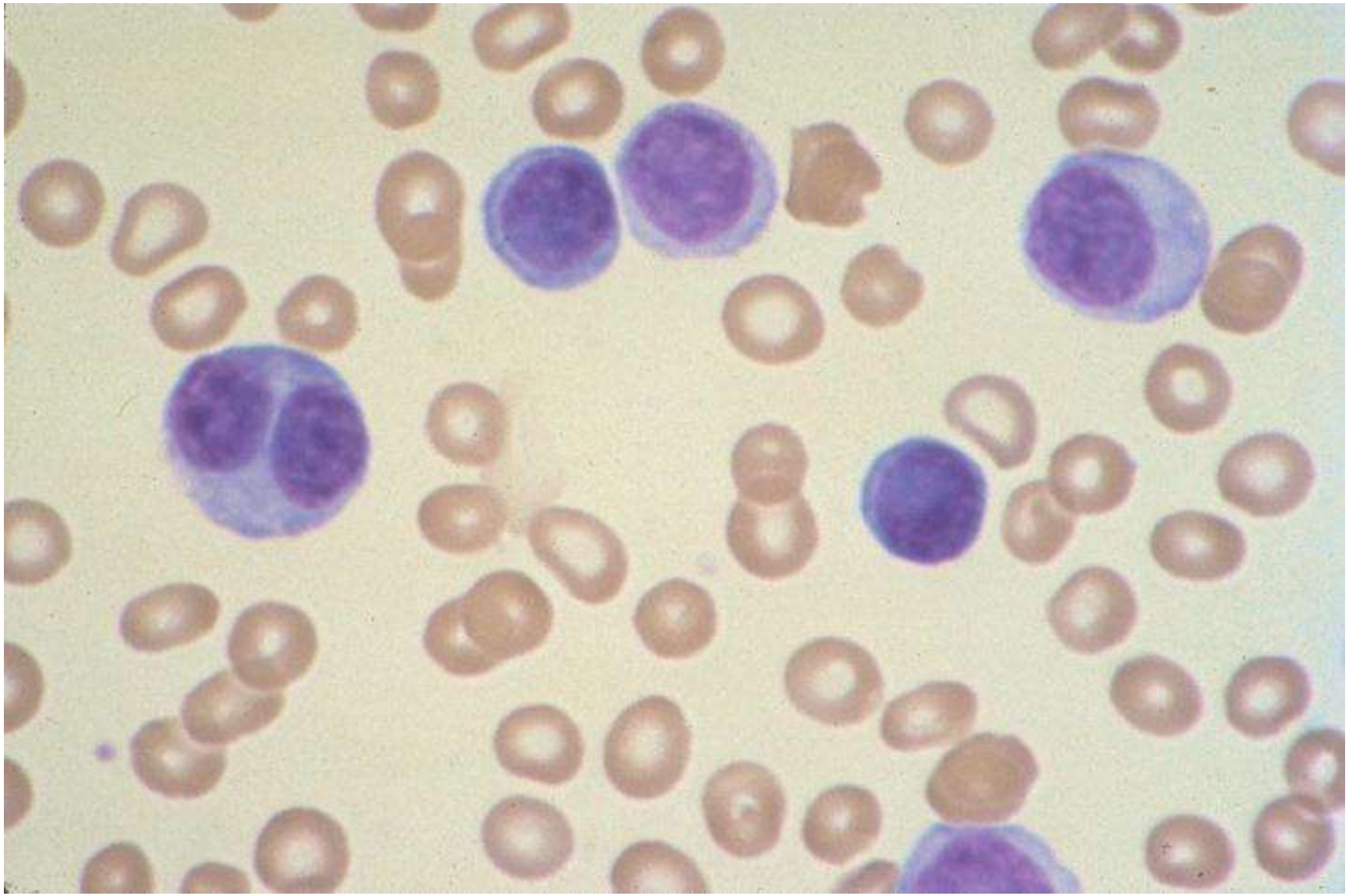
1. Late complication of MM or,
2. Primary disease

PCL is diagnosed by:

The presence of clonal plasma cells **≥ 2 × 10^9/L**, **or ≥ 20%** of circulating WBCs in the peripheral blood.

Clinically; either resembling:

- **AL**; Pancytopenia, organomegaly OR
- **MM**; Hypercalcemia, renal involvement, bone disease.



Plasma cell leukemia

A 64-year-old man presented with low backaches for six-month duration. CBC was normal. ESR was 120 mm/1st hour. On examination, there was no LAP or hepatosplenomegaly. The blood film shows marked rouleaux formation. Serum protein electrophoresis showed an M-band. Skull X-ray illustrated multiple punched-out bone lesions.

The most likely diagnosis is:

A. Acute lymphoblastic leukemia.
B. Chronic lymphocytic leukemia.
C. MGUS.
D. Multiple myeloma.

Case Scenario

A 56-year-old lady

- Suffered a severe pain in her left arm while pushing the oven in her kitchen.
- Also she had been complaining of low back pain for about 6 months.

On examination:

- Fever of 38°C.
- She was pale and dehydrated.
- She had a marked kyphosis.

What laboratory investigations should be ordered?

- Full Blood Count.
- Blood Film.
- Biochemical Tests.
- Radiological Study.

Full Blood Counts:

	Patient's Results	Normal Range
Hb	8.5 g/dL	12.5–16.5 g/dL
MCV	90.0 fL	80 – 96 fL
WBC count	11.6 × 10^9/L	4 – 11 × 10^9/L
Neutrophil count	8.2 × 10^9/L	2 – 7 × 10^9/L
Platelet count	160 × 10^9/L	150–400 × 10^9/L

▶Blood Film showing rouleaux formation (R).

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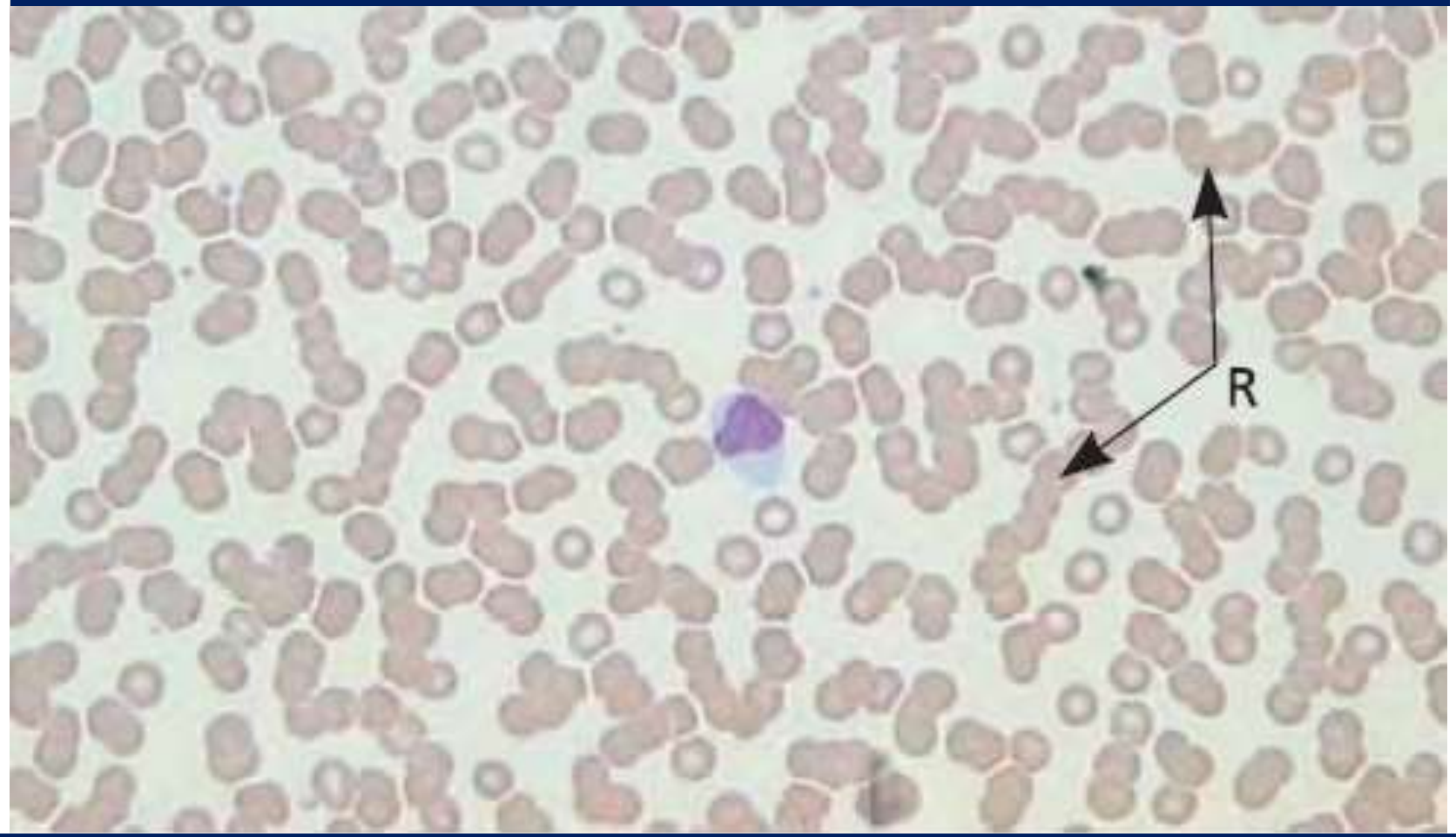


‘Rouleaux’ formation: The RBCs appear like coins stacked upon each other.

This happens because the red cells are covered with:

●Fibrinogen or ●Immunoglobulins

which inhibit the charges that usually makes red cells repel each other.

Biochemical Tests

Serum	Patient's Results	Normal Range
Creatinine	215 µmol/L	50–115 µmol/L
Calcium	3.36 mmol/L	2.20–2.70 mmol/L
Total Protein	95.5 g/L	60–80 g/L
Albumin	26.0 g/L	35–50 g/L

What other blood tests should be performed to confirm your suspicions?

Measurement of Serum Immunoglobulins.

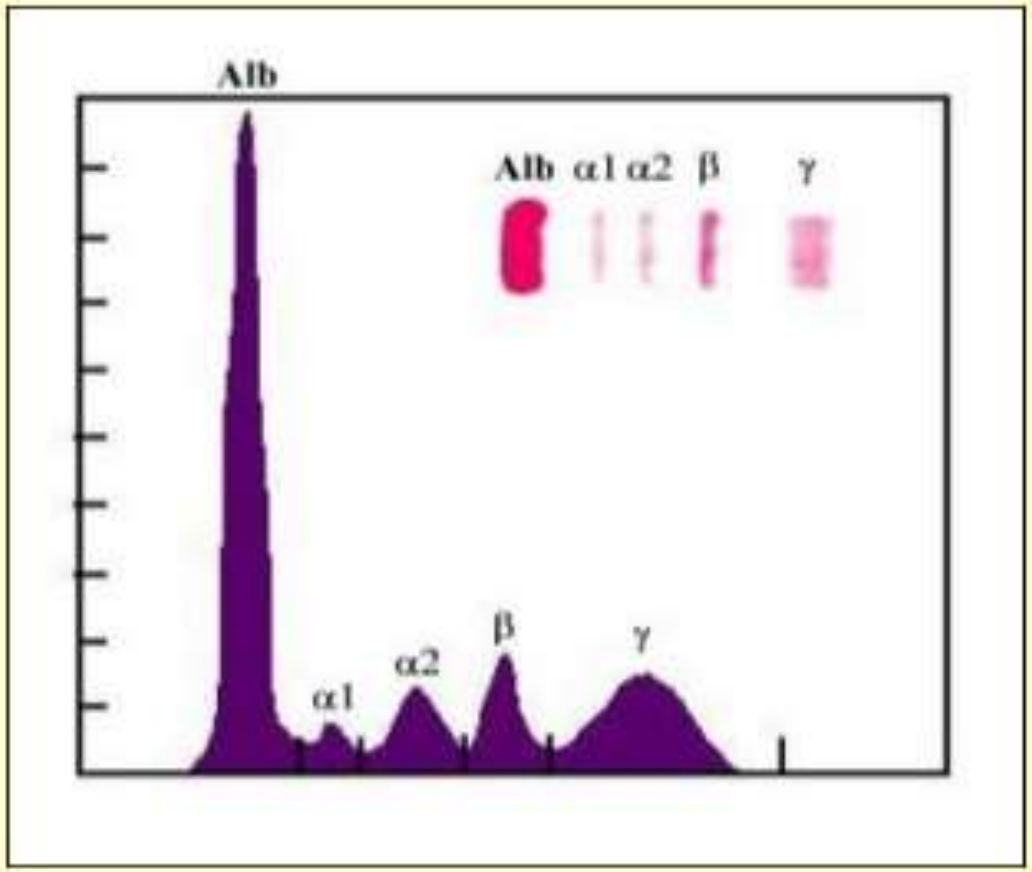
Serum Immunoglobulins	Patient's Results	Normal range
IgG	66.0 g/L	6.40–15.22 g/L
IgA	0.20 g/L	0.48–3.44 g/L
IgM	0.15 g/L	0.29–1.86 g/L

What further tests should be performed?

- Serum protein electrophoresis (SPE).
- Urine protein electrophoresis.

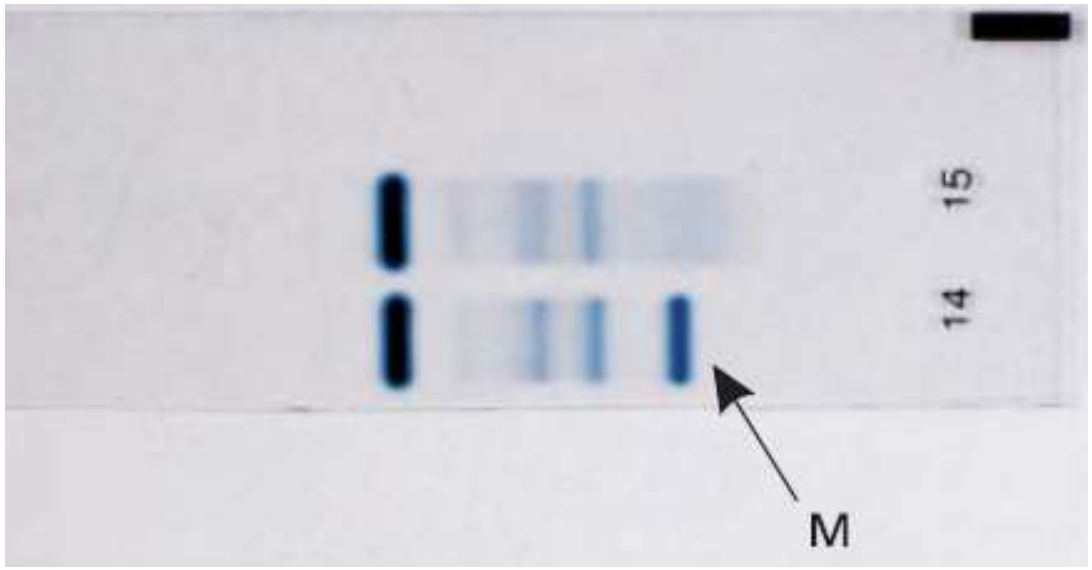
Serum proteins electrophoresis in diagnostics of diseases

Normal pattern

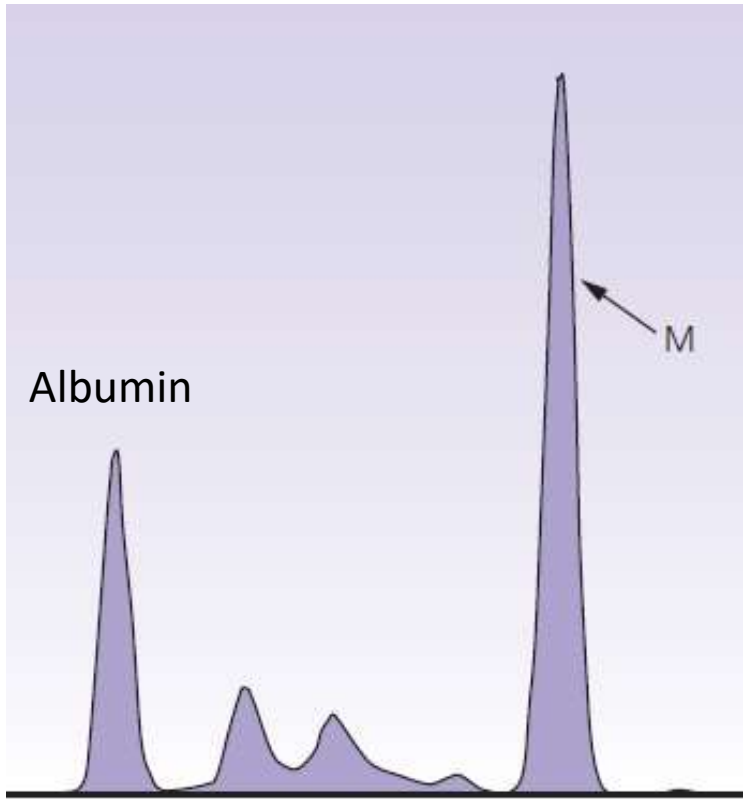


Reference ranges:

Total protein	6.0 - 8.0 g/dL
Albumin	3.5 - 5.0 g/dL
α1-globulins	0.1 - 0.4 g/dL
α2-globulins	0.4 - 1.3 g/dL
β-globulins	0.6 - 1.3 g/dL
γ-globulins	0.6 - 1.5 g/dL



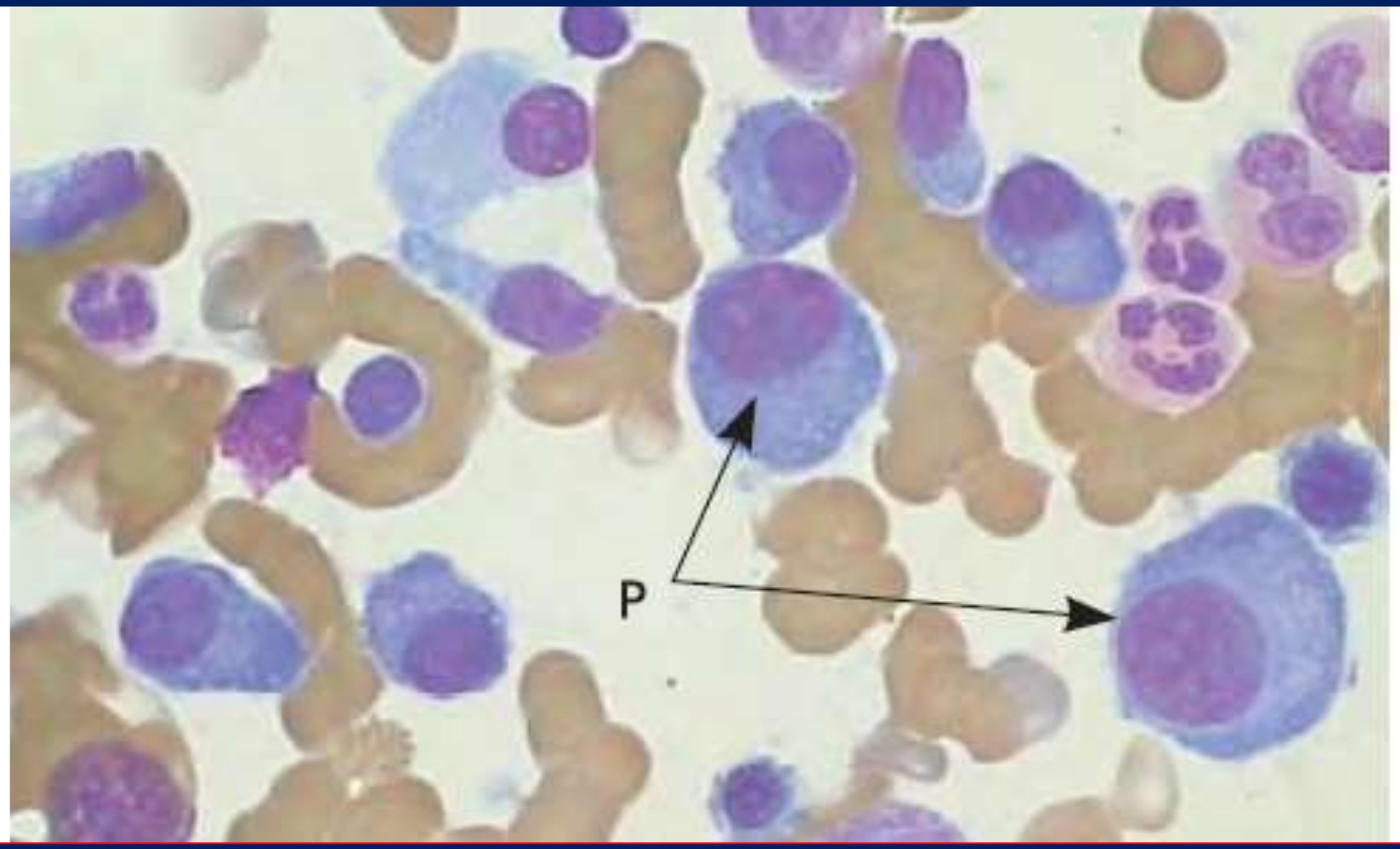
SPE: Proteins are placed on a supporting matrix and separated according to size and charge. The dense staining in the immunoglobulin region suggests that there is a monoclonal protein present (M).



Densitometery scan of the serum proteins. (M) Monoclonal Band.

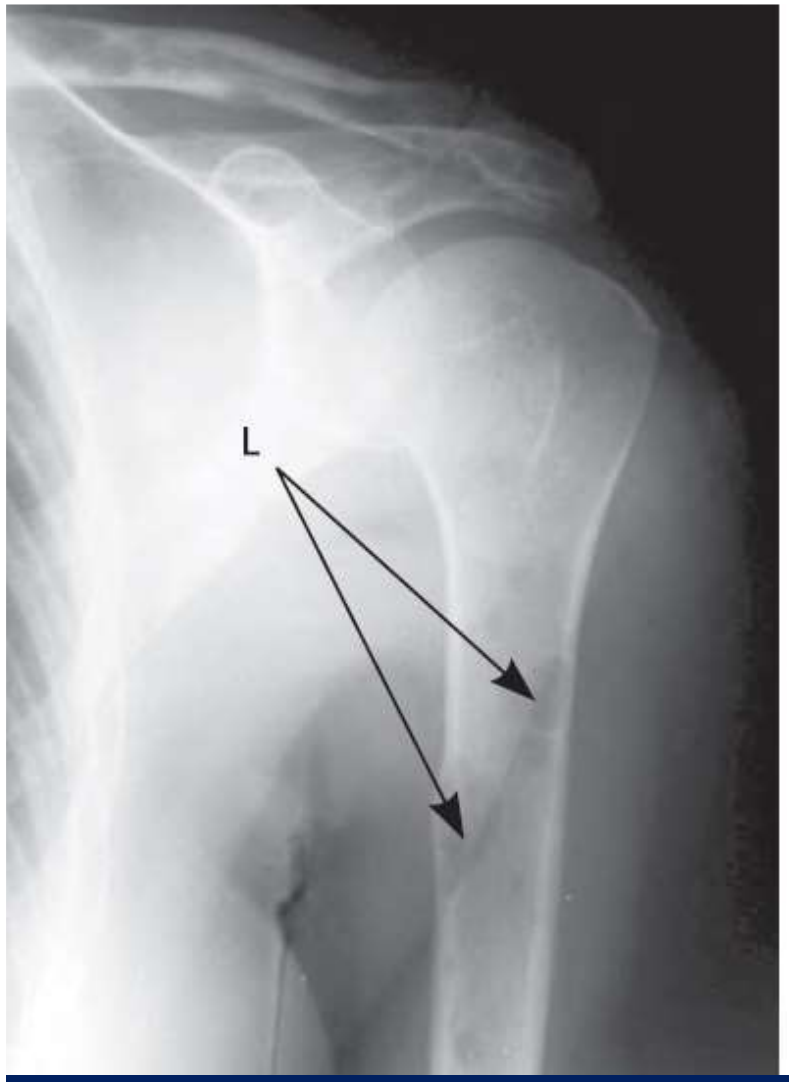
What other investigations should be performed to complete the diagnosis?

- **Bone Marrow Aspirate.**

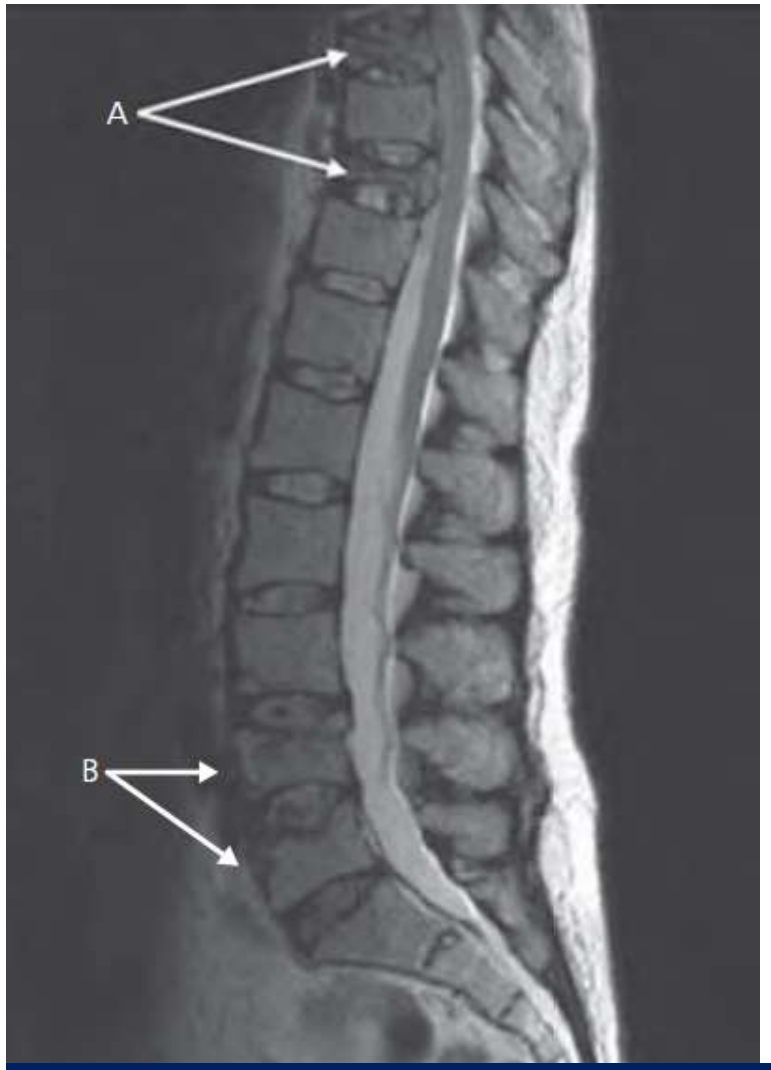


A Bone marrow aspirate showing multiple plasma cells (P) with dark blue cytoplasm and eccentric nucleus.

▶Radiological Studies



A radiograph showing multiple lytic lesions in the humerus (L).



Pathological compression fractures of T8 and T10 (A)

Summary

- Malignant plasma cells in MM, more commonly, produce both serum M components and BJP in urine.
- Presence of clonal BM plasma cells at least 10% or more or plasmacytoma on biopsy is essential for the diagnosis of MM.
- Presence of 60% or more clonal plasma cells in the BM is a sufficient single criterion for the diagnosis of MM.
- About 1-3% of MM patients have non-secretory plasma cells and do not show M-band.
- About 20% of patients do not have bone lesions.
- PCL diagnosis is based on the presence of 20% clonal plasma cells in the PB and not in the BM.

THANK YOU