Pathology

# Pathology sheet

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Multiple myeloma (MM) & related disorders

Plasma cell neoplasms

- Six major variants:
  1. Multiple myeloma (the big picture)
  2. Solitary plasmacytoma
  3. Lymphoplasmacytic lymphoma
  4. Heavy-chain disease
  5. Primary amyloidosis
could be alone (primary) but mostly we'll talk about amyloidosis which is part of MM and in this case it's called AL amyloidosis (light chain amyloidosis).
  6. MGUS... = monoclonal gammopathy of undetermined significance...when we find M protein in normal elderly persons

MM, overview

- Mean age: 70 years
- More in males and Africans
- Principally involves the bone marrow
- Causes lytic lesions throughout the skeleton

They secrete a single complete or partial immunoglobulin (abnormal)
...can be secreted in serum, so called: monoclonal gammopathies
...mostly M protein
Complete immunoglobulin = heavy chain + light chain
Partial = heavy chain alone or light chain alone
• Production of M protein (as we said if it’s secreted in the serum we call it monoclonal gammopathy)

...mainly of IgG type (and could be other types)

• In 15-20%: only lambda or kappa light chains are produced

...excreted in urine...called: Bence Jones proteins

Usually MM produce complete protein but in 15-20% they produce only light chain (lambda or kappa)

• More commonly MM produce both light chains and complete immunoglobulins (M protein)

  بنقطر نكشف عن M protein ومن lekker M protein
  و في ال bence jones proteins

Solitary plasmacytoma

• When it forms only a mass in bone or soft tissue

• Transform into multiple myeloma (bone marrow and blood involvement) over 5-10 years

• Modestly elevated M proteins are present in some cases at diagnosis

• Those of soft tissues: less likely to transform
As with most other B cell malignancies, myelomas often have chromosomal translocations involving the IgH locus on chromosome 14 and various other genes, including cyclin D1, fibroblast growth factor receptor 3, and cyclin D3 genes. Later in the course, translocations involving MYC are sometimes also observed. As might be surmised from this list of genes, dysregulation of D cyclins is common in multiple myeloma.

Mainly overexpression of cyclin D (which is important for the cell enter cell cycle)

**MM, bone lytic lesions**

- The characteristic bone resorption results from the secretion of certain cytokines (e.g., IL-1β, tumor necrosis factor, IL-6) by myeloma cells

...These cytokines stimulate production of another cytokine called RANK-ligand, which stimulates the differentiation and absorptive activity of osteoclasts

و في هذه الحالة العظم يصبح سهل الكسر تسمى هذه الحالة pathologic fracture

**MM, immunosuppression**

- Although the plasma usually contains increased immunoglobulin owing to the presence of an M protein, the levels of functional antibodies often are profoundly depressed, leaving patients at high risk for bacterial infections

بما أنه صار في افراز ل abnormal immunoglobulin
MM, renal dysfunction is a common, serious problem in myeloma

Bence Jones proteins بسبب التباث ال

• Mostly due to obstructive proteinaceous casts (high amount of proteins in urine appear as eosinophilic material), which often form in the distal convoluted tubules and the collecting ducts

...The casts consist mostly of Bence Jones proteins along with variable amounts of complete immunoglobulins, Tamm-Horsfall protein, and albumin

• Light chain deposition in the glomeruli or the interstitium

...either as amyloid (insoluble form) or linear deposits

...also may contribute to renal dysfunction

Once you see Renal failure & anemia & hypercalcemia in old people think about Multiple myeloma.

MM, renal dysfunction, cont’d

• Hypercalcemia, which may lead to dehydration and renal stones

• Frequent bouts of bacterial pyelonephritis, which stem in part from the hypogammaglobulinemia

Lower urinary tract infection could reach the ureter and the kidney which is called ascending pyelonephritis (pyelo → ureter, nephritis → kidney) because these patients are immunocompromised and this will cause more damage to the kidney.
MM, clinical manifestations

- **Bone pain**, due to pathologic fractures. Pathologic fractures of vertebrae may lead to spinal cord impingement, an oncologic emergency.
- **Hypercalcemia** stemming from bone resorption leads to neurologic manifestations such as confusion and lethargy and contributes to renal dysfunction.
- **Anemia**, due to marrow replacement by tumor cells as well as suppression of hematopoiesis through uncertain mechanisms.
- **Recurrent infections** with bacteria such as *S. aureus*, *S. pneumoniae*, and *E. coli*, resulting from the marked suppression of normal humoral immunity.
- **Renal insufficiency** (in up to 50% of patients), resulting from the deleterious effect of Bence Jones proteins on renal tubular cells, as well as bacterial infections, hypercalcemia, and amyloidosis.
- **AL-type amyloidosis** (5% to 10% of patients)
- Symptoms related to hyperviscosity may occur owing to excessive production and aggregation of M proteins but this clinical presentation is much more characteristic of lymphoplasmacytic lymphoma.

Viscosity in MM is less than that in lymphoplasmacytic lymphoma because MM produce mainly IgG which doesn’t cause very high viscosity in blood unlike IgM that is produced in lymphoplasmacytic lymphoma.
**MM, diagnostic tests**

- Serum and urine electrophoresis

As we said serum electrophoresis for M protein and urine electrophoresis for bence jones proteins (and also for M protein)

...in 99% of cases, either a monoclonal complete immunoglobulin or a monoclonal free immunoglobulin light chain is present in the serum, the urine, or both

...sometimes: nonsecretory and only detected in plasma cells (immunohistochemistry for plasma cells) in these cases it’s called nonsecretory multiple myeloma

- Bone marrow: increased plasma cells

**MGUS**

Monoclonal Gammopathy of Undetermined Significance

- M proteins are found in the serum of 1% to 3% of otherwise healthy persons older than age 50 years

  ...the most common plasma cell proliferation

- A precursor of MM...1% per year (could transform to MM)

- Similar chromosomal translocations to MM

- Patients with MGUS have less than 3 g/dL of monoclonal protein in the serum and no Bence Jones proteinuria
There are criteria to diagnose MM like lytic lesion in bones, proteins in serum and urine (M protein & Bence Jones proteins), increased plasma cells in bone marrow, and renal failure as we said.

Smoldering myeloma or asymptomatic myeloma

Lymphoplasmacytic lymphoma

- Peak incidence is between 6\textsuperscript{th} and 7\textsuperscript{th} decade (old age)
- Secrete M proteins...mostly IgM (macroglobulin)
- The tumor is a mixture of small B lymphocytes, plasmacytic lymphocytes (lymphocytes that look like plasma cells) and plasma cells
- An indolent lymphoma with common involvement of Lymph Nodes, spleen & bone marrow
**Lymphoplasmacytic lymphoma, cont’d**

- The high levels of IgM cause the blood to become **viscous** producing a syndrome called Waldenstrom macroglobulinemia.

- Unlike multiple myeloma:
  - no free light chains or Bence Jones proteinuria
  - no lytic bone lesions
  - only rarely associated with amyloidosis

**Lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia**

- Visual impairment due to: retinal vascular changes...**vessels become tortuous with hemorrhage**

- Neurologic problems...due to sluggish blood flow

- Bleeding...due to IgM interfering with clotting factors & platelets

- Cryoglobulinemia...precipitation of IgM on endothelial surface at low temperature (**like fingers and nose etc**) will cause Raynaud phenomenon & cold urticarial (**changes on the skin**)