NOTES
PLASMA CELL DYSCRASIAS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Acquired/inherited disorders
  - Impaired platelet function, decreased platelet count, sequelae
- Accelerated destruction/consumption → decreased platelets

SIGNS & SYMPTOMS

- Mucocutaneous bleeding (e.g. epistaxis, gingival bleeding, petechiae, purpura)

DIAGNOSIS

LAB RESULTS

- Complete blood count (CBC)
- Peripheral blood smear analysis
- Platelet function tests

TREATMENT

OTHER INTERVENTIONS

- Mitigate complications of deranged platelet function

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

osms.it/monoclonal-gammopathy

PATHOLOGY & CAUSES

- Asymptomatic premalignant plasma cell proliferative disorder; M protein < 3g/dL
- Most common plasma cell dyscrasia
- M protein
  - IgM, IgA, IgG of free light chains
- 25% progress to multiple myeloma, early stage

TYPES

- Non-IgM MGUS (IgG, IgA, IgD MGUS)
- IgM MGUS

CAUSES

Genetic mutations

- t(14,11)
  - Translocation between Ig heavy chain gene on chromosome 14, oncogene (cyclin D1) on chromosome 11
- t(14,6)
  - Translocation between Ig heavy chain gene on chromosome 14, oncogene cyclin D3 on chromosome 6
- Deletion of gene TP53 tumor suppressor locus on chromosome 17

RISK FACTORS

- More commons in individuals who are biologically male; increased incidence with age
- Agent Orange exposure

COMPLICATIONS

- Multiple myeloma (IgA, IgG MGUS), Waldenström macroglobulinemia, AL amyloidosis, light chain deposition disease (IgM MGUS)
- Venous thromboembolism (VTE), fractures, infections

SIGNS & SYMPTOMS

- Mostly asymptomatic
- Rash, paresthesias, hypoesthesia

DIAGNOSIS

LAB RESULTS

- Monoclonal proteins < 3mg/dL
- Plasma cells CD38+, CD56+, CD19-

Bone marrow biopsy

- Mild hypercellularity
  - Plasma cells < 10%

TREATMENT

OTHER INTERVENTIONS

- No treatment
- Regular observation; assess progression

MULTIPLE MYELOMA

osms.it/multiple-myeloma

PATHOLOGY & CAUSES

- Neoplasm of plasma cells (myeloma cells) in bone marrow
  - Overproduction of M protein
- M protein
  - IgG, IgA, free light chains
- Bone marrow cells, myeloma cells secrete cytokines, interleukin 6 (IL6), NF-κB → promote proliferation, survival of myeloma cells

MNEMONIC: CRAB

Features of Multiple myeloma

Calcium elevated
Renal disease
Anemia
Bone lesions

Calcium (elevated)

- Increased bone resorption → hypercalcemia

Renal disease

- Monoclonal free light chains (κ, λ)
  - Low molecular mass, filter easily in renal glomeruli → Bence Jones proteins in urine, toxic to proximal tubules → proximal tubular necrosis
  - Bence Jones, Tamm-Horsfall proteins, albumin form obstructive proteinaceous casts in distal convoluted tubules, collecting ducts
  - Hypercalcemia, hypercalciuria → nephrocalcinosis

Anemia

- Neutropenia, thrombocytopenia
- Bone marrow infiltration by myeloma cells, cytokines → inhibits hematopoiesis

Bone lesions (osteolytic)

- Neoplastic cells secrete cytokines (IL1β, TNFα) → activate osteoclasts → increase bone resorption → hypercalcemia,

pathologic fractures
- Axial skeleton (skull, spinal vertebrae, ribs, pelvic bones), long bones
- Pathologic fractures along vertebrae → spinal cord compression

TYPES

Smoldering multiple myeloma (SMM)
- Asymptomatic

Symptomatic multiple myeloma

Non-secretory multiple myeloma
- Less common (3%)

CAUSES

Genetic mutations
- t(14,11)
  - Translocation between Ig heavy chain gene on chromosome 14, oncogene (cyclin D1) on chromosome 11
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- Deletion of gene *TP53* tumor suppressor locus on chromosome 17

RISK FACTORS
- Alcohol consumption, obesity, radiation exposure, family history

COMPLICATIONS
- Free light chains deposit in kidneys, heart, other organs → immunoglobulin light chain amyloidosis (AL amyloidosis)
- Renal failure
- Infection → death
  - Most common, urinary tract infections (UTIs); pneumonia
- Hyperviscosity syndrome

SIGNS & SYMPTOMS
- Hypercalcemia
  - Confusion, somnolence, constipation, nausea, thirst
- Anemia, neutropenia, thrombocytopenia
  - Fatigue, pallor, fever, infections, bleeding
- Bone lesions
  - Pain, pathologic fractures; spinal cord compression → neuropathies (hypoesthesia, paresthesia)

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray (skeletal survey)
- Multiple rounded lytic bone lesions in skull, long bones, spine

CT scan
- Radiodense bone lesions; in advanced disease, lesions in spleen, lymph nodes, lungs, etc.

MRI
- Radiodense lesions in thoracic, lumbar vertebrae

Fluorescent in situ hybridization (FISH)
- Detection of chromosomal mutations (translocations, deletions)

LAB RESULTS
- Cormocytic, normochromic anemia, thrombocytopenia, leukopenia
- Increased monoclonal proteins (free light chains, ↑IgG > 3mg/dL, ↑IgA)
- Monoclonal protein measurement with densitometer
- Calcium blood test
  - > 2.7mmol/L
- Bence Jones proteins (> 6mg/dL)
- Quantification of Bence Jones proteins
- Proteinuria greater than 1g/24hr
- Myeloma cells CD36+, CD56+, CD138+, CD319+

Bone marrow biopsy

- Neoplastic infiltration → hypercellularity (> 30% plasma cells)
- Cytology
  - *Plasma cells:* 2–3 times larger, eccentric nuclei, perinuclear halo (prominent Golgi apparatus)
  - *Other variants:* mott cells (multiple grapelike cytoplasmic inclusions), flame cells (fiery red cytoplasm)

TREATMENT

- Treatable, incurable
  - If untreated, survival 5–12 months; with treatment, 48% survival for five years

MEDICATIONS

- Chemotherapy
  - Bortezomib, lenalidomide–dexamethasone, melphalan
- Immunomodulators
  - Thalidomide, lenalidomide
- *Bisphosphonates:* prevent bone loss
- *Antibiotics:* infections
- *Glucocorticoids:* hypercalcemia

OTHER INTERVENTIONS

- Autologous hematopoietic stem-cell transplantation (ASCT)
- Allogeneic stem cell transplantation with chemotherapy, glucocorticoids

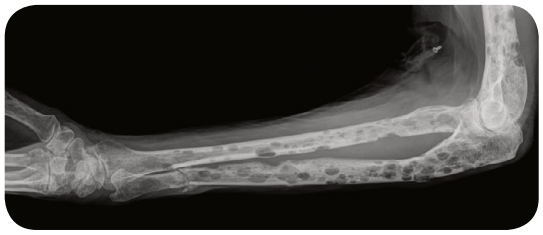

Figure 55.3 An X-ray image of the forearm demonstrating multiple lytic lesions in an individual with multiple myeloma.

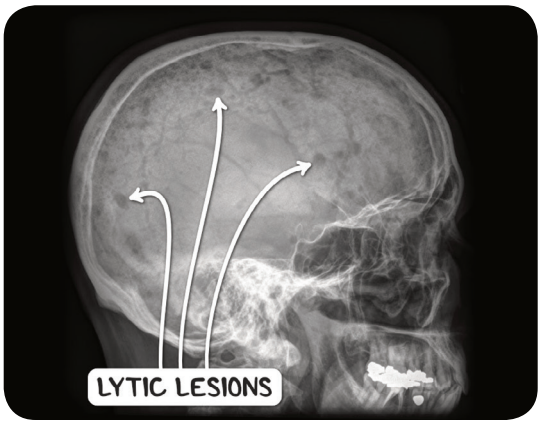

Figure 55.1 An X-ray image of the skull displaying numerous lytic lesions caused by myelomatous deposits. This radiological presentation is commonly known as a pepper pot skull.

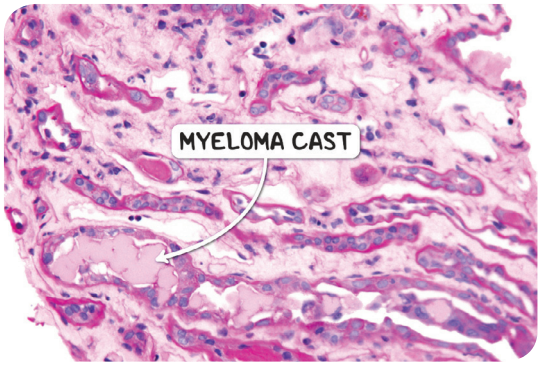

Figure 55.2 A histological section of the kidney from an individual with multiple myeloma. The myeloma cast colors a light pink on PAS stain.

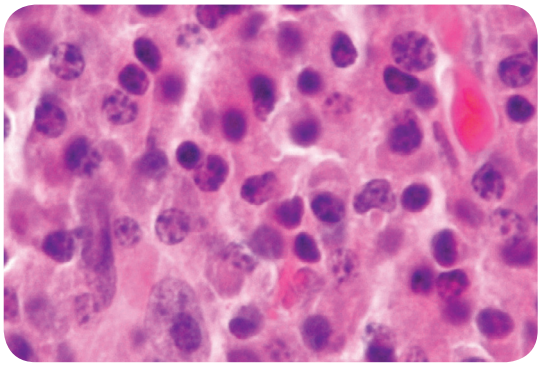

Figure 55.4 The histological appearance of a plasmacytoma, an aggregate of malignant plasma cells found in the soft tissues or axial skeleton.

WALDENSTRÖM MACROGLOBULINEMIA

osms.it/waldenstrom-macroglobulinemia

PATHOLOGY & CAUSES

- Neoplasm of plasma cells, lymphoplasmacytoid cells; high levels of M protein as IgM antibodies
- AKA lymphoplasmacytic lymphoma
- Preceded by MGUS
- Neoplastic plasma, lymphoplasmacytoid cells infiltrate, crowd out normal hematopoietic cells → anemia
- High levels of IgM antibodies aggregate
  - Hyperviscosity syndrome
  - *Cryoglobulinemia:* IgM proteins become insoluble at reduced temperatures

CAUSES

- Somatic mutations of *MYD88*, *CXCR4* genes

RISK FACTORS

- Autoimmune diseases mediated by antibodies
- HIV, hepatitis, rickettsiosis
- Pesticides exposure

COMPLICATIONS

- Autoimmune hemolysis, raynaud phenomenon secondary to cryoglobulinemia
- Amyloidosis of heart, kidney, liver, lungs, joints

SIGNS & SYMPTOMS

- Infiltration of neoplastic plasma cells
  - Splenomegaly, hepatomegaly, lymphadenopathy
- Anemia
  - Weakness, fatigue, weight loss

Hyperviscosity syndrome triad

- Retinopathy
  - Stasis + venous congestion, distention, hemorrhage of retinal veins → vision loss
- Neurologic symptoms
  - Venous congestion of cerebral veins → hypoperfusion → headache, vertigo, hearing loss, parestesias, ataxia, stupor
- Mucosal bleeding
  - IgM antibodies interfere with coagulation → gum bleeding, epistaxis, rectal bleeding, menorrhagia

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Hepatomegaly, splenomegaly

LAB RESULTS

- Normocytic, normochromic anemia
- IgM ≥ 3000mg/dL

TREATMENT

- If asymptomatic, observation

MEDICATIONS

- Chemotherapy
- Plasmapheresis for hyperviscosity syndrome

OTHER INTERVENTIONS

- Rarely autologous stem cell transplantation

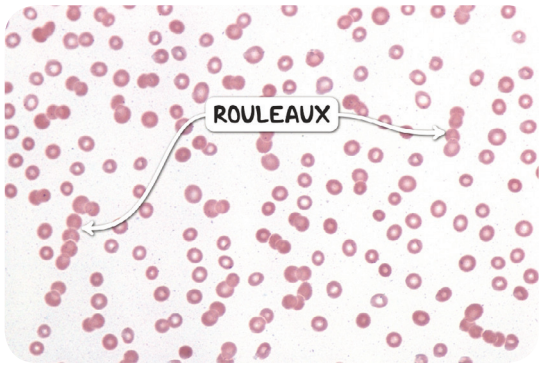

Figure 55.5 A peripheral blood film demonstrating rouleaux formation. Rouleaux may be seen in many infections, autoimmune conditions and plasma cell diseases, including Waldenstrom macroglobulinemia.