NOTES
DYSPLASTIC & PROLIFERATIVE DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Acquired disorders caused by defective hematopoiesis

CAUSES

- Mostly idiopathic
- Gene mutations
  - JAK2 gene in most myeloproliferative disorders

COMPLICATIONS

- Can progress to serious conditions
  - Acute myelogenous leukemia (AML)

SIGNS & SYMPTOMS

- Can be asymptomatic
- When symptomatic, depends on cell line affected

DIAGNOSIS

LAB RESULTS

- Complete blood count (CBC)
  - Cell line levels
- Peripheral blood smear
  - Morphology
- Bone marrow aspiration/biopsy
  - Morphology, cellularity (normal, hypo, hyper), % of blasts
- Cytogenetic studies
  - Chromosomal abnormalities
- Molecular tests
  - Gene mutations

TREATMENT

OTHER INTERVENTIONS

- Blood transfusion
- Hematopoietic stem cell transplant

ESSENTIAL THROMBOCYTOSIS

osms.it/essential-thrombocytosis

PATHOLOGY & CAUSES

- Chronic myeloproliferative neoplasm due to overproduction of megakaryocytes in bone marrow
- AKA essential thrombocythemia
- ↑ platelets, abnormally shaped; ↓ platelet survival
- Thromboses; bleeding episodes may occur; other cell lines may be affected
- *JAK2* mutation (50%), *MPL* (5–10%)/ calreticulin
- "Spent phase" of myelofibrosis/AML (rarely)

SIGNS & SYMPTOMS

- Primary symptomatic manifestations due to thrombosis → potential ischemia in various organs, extremities (e.g. stroke, erythromelalgia)
- Headache, dizziness, fatigue, vision loss, abdominal pain, nausea
- Less frequently, paradoxical bleeding
  - Epistaxis, bleeding gums, ecchymoses
- Splenomegaly

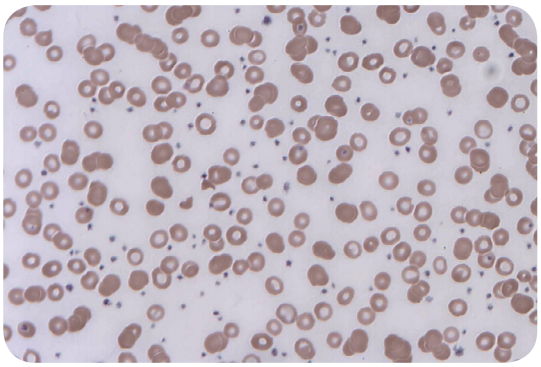

Figure 45.1 A peripheral blood smear from an individual with essential thrombocytosis. There are a higher than normal number of platelets visible.

DIAGNOSIS

LAB RESULTS

- Platelets > 450 × 103/μL for ≥ two months; anisocytosis
- ↑ bleeding time

Bone marrow aspiration/biopsy

- Normal cellularity

Genetic testing

- *JAK2* mutation

OTHER DIAGNOSTCS

- History of thrombosis, bleeding, vasomotor symptoms, first trimester fetal loss

TREATMENT

MEDICATIONS

- Low risk for thrombosis
  - Antiplatelet drugs (aspirin, anagrelide)
- High risk for thrombosis
  - Hydroxyurea, interferon-alpha

SURGERY

- In severe conditions
  - Plateletpheresis (removal of platelets from blood)

LANGERHANS CELL HISTIOCYTOSIS (LCH)

osms.it/langerhans-cell-histiocytosis

PATHOLOGY & CAUSES

- Rare, proliferative disorder affecting Langerhans cells (type of dendritic cells), myeloid progenitor cells in bone marrow
- AKA histiocytosis X
- Osteolytic bone lesions infiltrated with histiocytes; histiocytes, lymphocytes, macrophages, eosinophils infiltrate organs: skin, lymph nodes, bones, lungs, liver, spleen, central nervous system (CNS)

Proliferating cells

- Functionally immature
- Immunohistochemistry
  - CD1a, S100 positive
- Abundant, foamy cytoplasm
- Folded, grooved nuclei
- Birbeck granules, "tennis racket"/rod-shaped cytoplasmic organelles

RISK FACTORS

- Usually affects children; also present in adults
- Mutations detected; most common (55–60%) activates *BRAF* gene

COMPLICATIONS

- CNS
  - Pituitary gland → diabetes insipidus, pons, basal ganglia; cerebellum → cognitive deficits, neuromotor dysfunction
- Liver, spleen
  - Worse prognosis; sclerosing cholangitis may require liver transplant

SIGNS & SYMPTOMS

- Lytic bone lesions may be asymptomatic/cause localized pain
- Skin lesions
  - Brown to purplish papules pustular, purpuric, petechial, vesicular, papulo-nodular; eczema-like rash
- Mucous membranes
  - Gingivitis, mucosal mass/ulcers, loose teeth
- Lymphadenopathy
- Liver, spleen
  - Hepatic lesions, hepatosplenomegaly
- Lungs
  - Recurrent spontaneous pneumothorax, dyspnoea, chest pain
- CNS
  - Diabetes insipidus, neurological deficits
- Systematic symptoms
  - Fever, lethargy, weight loss

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- CNS involvement

LAB RESULTS

- Accumulation of inflammatory cells, Langerhans cells (large, mononuclear cells with prominent nuclear groove), few cytoplasmic vacuoles, pale eosinophilic cytoplasm

TREATMENT

- Spontaneous regression can occur

MEDICATIONS

- Systemic corticosteroids
- Chemotherapeutic agents
  - Alkylating agents, antimetabolites, vinca alkaloids

SURGERY

- Surgial excision

OTHER INTERVENTIONS

- Radiation therapy

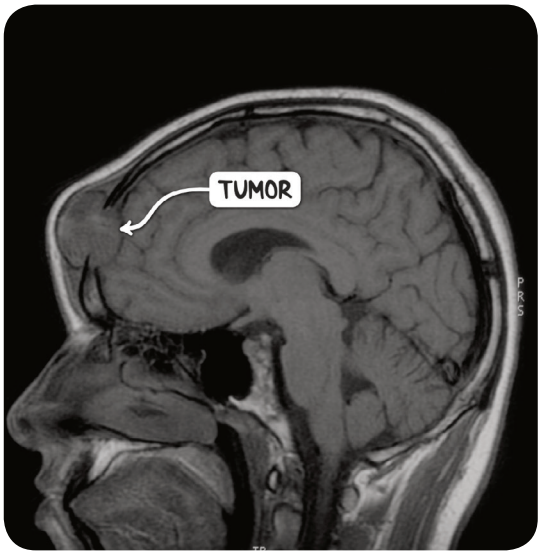

Figure 45.3 An MRI scan of the head in the sagittal plane demonstrating a subcutaneous soft-tissue mass, destroying the frontal bone. The diagnosis was confirmed as Langerhans histiocytosis on biopsy.

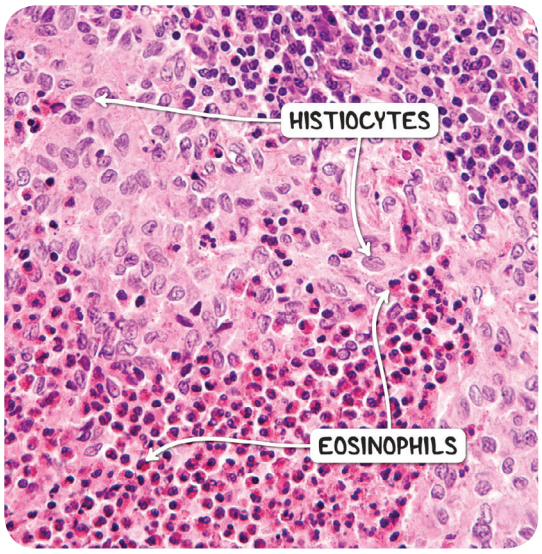

Figure 45.2 The histological appearance of Langerhans cell histiocytosis. There are numerous clonal dendritic cells (light pink) with associated eosinophils (red).

LEUKEMOID REACTION

osms.it/leukemoid-reaction

PATHOLOGY & CAUSES

- Excessive, reactive leukocytosis (WBCs: 40,000–100,000/mL), resembling leukemia, with increase in neutrophil precursors, "left shift" (e.g. myeloblasts, promyelocytes, myelocytes) in peripheral blood
- Cytoplasmic toxic granulation, Dohle bodies, blue-gray inclusions in peripheral cytoplasm of neutrophils
- Lymphocytic reaction can occur

COMPLICATIONS

- Severe/chronic infections
  - *Clostridium difficile* infection (CDI), *Mycobacterium tuberculosis*, *Bordetella pertussis*, Epstein–Barr virus (EBV)
- Sepsis
- Non-infectious inflammation
  - Burns, postoperative state, acute asthma attack, acute episodes of gout
- Severe hemolysis
- Acute hemorrhage
  - Peritoneal cavity
- Tissue necrosis
  - Hepatic necrosis, ischemic colitis
- Metastatic cancer
- Paraneoplastic syndrome
  - Lung carcinoma, renal cell carcinoma
- Drugs
  - Sulfonamides, dapsone, glucocorticosteroids, granulocyte-colony stimulating factor (G-CSF)
- Asplenia
- Metabolic
  - Diabetic ketoacidosis, preeclampsia, uremia

SIGNS & SYMPTOMS

- Fatigue, weakness, high fever

DIAGNOSIS

LAB RESULTS

- ↑↑↑ WBCs
- Rule out blood malignancies
  - Mature neutrophil precursors, unlike immature cells in acute leukemia (blasts < 20%); toxic granulation, Döhle bodies unlike chronic myelogenous leukemia (CML)
  - Serum leukocyte alkaline phosphatase (LAP) score normal/elevated, unlike CML
  - Confirm CML by Philadelphia chromosome with *BCR/ABL* fusion gene + *FISH/PCR*
  - Bone marrow aspiration/biopsy

TREATMENT

- Treatment of underlying condition

MYELODYSPLASTIC SYNDROMES (MDS)

osms.it/myelodysplastic-syndrome

PATHOLOGY & CAUSES

- Group of malignant hematopoietic stem cell disorders
- Abnormal, ineffective hematopoiesis → peripheral cytopenia

Dysplastic cells

- Pseudo Pelger–Huët cells
  - Bilobed neutrophils
- Ring sideroblasts
  - Erythroblasts with granules of iron accumulated in mitochondria
- Megaloblastoid maturation
- Nuclear budding abnormalities
- Pawn ball megakaryocytes
  - Discrete nuclear lobes/multinucleation

CAUSES

- Can be idiopathic/secondary to exposure
  - Toxins, genotoxic drugs, immunosuppressive agents, chemotherapy, radiation therapy (t-MDS, therapy related MDS)
- Genetic defects due to
  - Epigenetic factors, RNA splicing factors, transcription factors
  - 5q (5q-) deletion most common
- Affects elderly individuals; mean age of onset is 70 years

COMPLICATIONS

- MDS = pre-leukemias, high risk of conversion to AML
- % of blasts (1–20%)
  - How close individual is to AML (> 20%)
- Progresses slowly → most succumb to bleeding, infections before AML
- Functional defects in red (RBCs), white blood cells (WBCs), platelets → anemia, infections, bleeding

SIGNS & SYMPTOMS

- Asymptomatic in early stages
- Fatigue (anemia), infections (neutropenia), bleeding (thrombocytopenia)

DIAGNOSIS

LAB RESULTS

- Low RBCs, WBCs, platelets, normal/mildly elevated mean corpuscular volume (MCV), increased red cell distribution width (RDW)
- Low reticulocyte count, dysplastic RBCs, WBCs, normal platelets, 1–20% blasts
- Dysplastic cells, increased blasts
- Chromosomal abnormalities, gene mutations

TREATMENT

MEDICATIONS

- Tumor necrosis factor (TNF) inhibitors (e.g.lenalidomide, thalidomide), DNA methylation inhibitors

OTHER INTERVENTIONS

Allogeneic hematopoietic stem cell transplant

- Only curative option, for young individuals
- If transplant not an option → blood product transfusions, infection control (supportive)

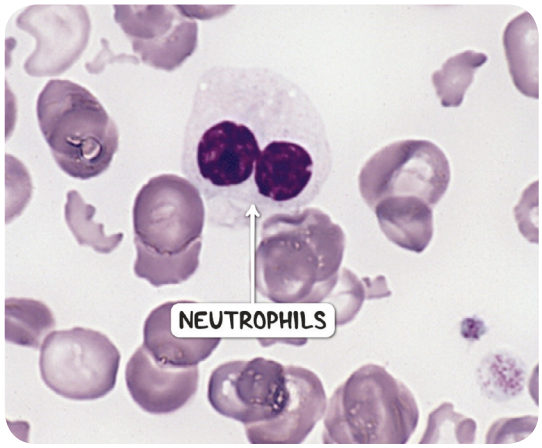

Figure 45.4 A neutrophil from a in the peripheral blood smear of an individual with myelodysplastic syndrome. The neutrophil is hypogranulated and has a hypolobated nucleus, known as a pseudo Pelger–Huët nucleus.

POLYCYTHEMIA VERA (PCV)

osms.it/polycythemia-vera

PATHOLOGY & CAUSES

- Chronic myeloproliferative neoplastic disease
- Hematopoietic stem cell disorder → erythroid, granulocytic, megakaryocytic lineages proliferate
- Increased
  - RBCs, independent of erythropoietin (EPO); platelets; basophils; eosinophils; cell turnover → hyperuricemia
- Polycythemia → increased blood viscosity; increased total blood volume → abnormal blood flow
- Abnormal blood flow, defective platelet function → vein thrombosis, infarcts, bleeding
- PCV may evolve to "spent phase"
  - Myelofibrosis, extramedullary hematopoiesis in liver, spleen

RISK FACTORS

- Occurs in all ages; median age at diagnosis 60 years
- Genetic
  - JAK2V617F mutation (95% of cases)

COMPLICATIONS

- Hypertension, Budd–Chiari syndrome, deep vein thrombosis, arterial thrombosis, myocardial infarction (MI), gout (high cell turnover, hyperuricemia), PCV → AML (rare)
- If untreated
  - Thrombotic, hemorrhagic complications → death within months

SIGNS & SYMPTOMS

- Symptoms due to ↑ in RBCs → blood viscosity
  - Headache, fatigue, dizziness, dyspnea, plethora, cyanosis
- Symptoms due to ↑ in basophils → histamine release
  - Pruritus (intense itching, especially after hot shower), gastric ulcers
- Thrombosis
  - Deep vein thrombosis, MI, Budd–Chiari syndrome (portal vein thrombosis), erythromelalgia (hyperemic and inflamed extremities due to microvascular occlusion of vessels)
- Bleeding
  - Bleeding gums, epistaxis, ecchymoses, GI bleed
- Hepatosplenomegaly, splenomegaly
- Hypertension

DIAGNOSIS

LAB RESULTS

- Exclude secondary polycythemia (hypoxia, renal cell, hepatocellular carcinoma); ↑ EPO serum
- CBC
  - ↑ RBCs, hematocrit, hemoglobin; ↑ platelets/WBCs
- ↑ Lactate dehydrogenase
- ↓ serum EPO
- Bone marrow aspiration/biopsy confirms diagnosis
- Genetic testing
  - *JAK2* mutation

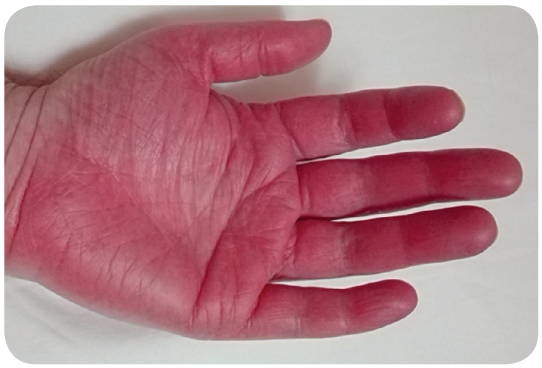

Figure 45.5 The clinical appearance of erythromelalgia; a sign of numerous diseases, including polycythemia vera.

TREATMENT

MEDICATIONS

- Hydroxyurea
  - ↓ RBC production
- Interferon-alpha
  - ↑ RBC destruction
- Aspirin
  - ↓ risk of thrombosis

OTHER INTERVENTIONS

- Phlebotomy
  - ↓ hematocrit, hemoglobin

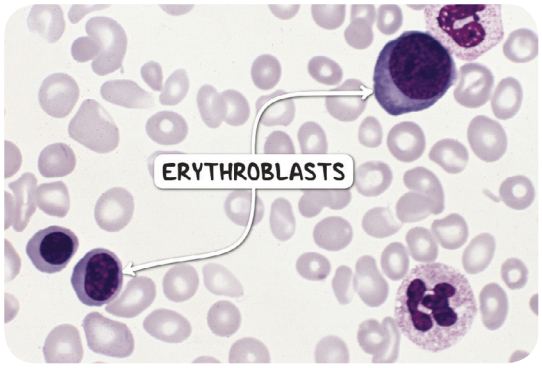

Figure 45.6 The clinical appearance of erythromelalgia; a sign of numerous diseases, including polycythemia vera.

PRIMARY MYELOFIBROSIS (PM)

osms.it/myelofibrosis

PATHOLOGY & CAUSES

- Chronic myeloproliferative disease of hematopoietic stem cells resulting in bone marrow fibrosis
- AKA essential thrombocythemia
- Overproduction of megakaryocytes in bone marrow
- Increased platelets, abnormally shaped; decreased platelet survival
- Thromboses; bleeding episodes may occur; other cell lines may be affected
- *JAK2* mutation (50%), *MPL* (5–10%)/ calreticulin
- "Spent phase" of myelofibrosis/AML (rarely)

SIGNS & SYMPTOMS

- May be asymptomatic
- When symptomatic, thrombosis, potential ischemia in various organs
  - Headache, dizziness, fatigue, numbness in extremities, erythromelalgia, vision loss, abdominal pain, nausea
- Less frequently, bleeding
  - Epistaxis, bleeding gums, bruises
- Splenomegaly

DIAGNOSIS

LAB RESULTS

- ↓ RBCs, platelets
- Leukoerythroblastosis, dacryocytes

Bone marrow biopsy

- Hypocellularity, fibrosis

OTHER INTERVENTIONS

Bone marrow aspiration

- Dry tap, no sample (accumulation of collagen fibers)

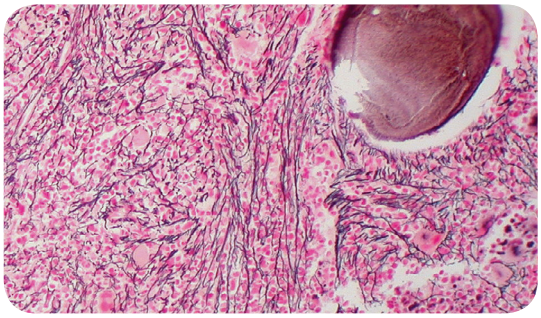

Figure 45.7 The histological appearance of the bone marrow in an individual with myelofibrosis. The fibrosis is seen as fine silver strands upon staining with reticulin.

TREATMENT

MEDICATIONS

- Low risk for thrombosis
  - Antiplatelet drugs (aspirin, anagrelide)
- High risk for thrombosis
  - Hydroxyurea, interferon-alpha

SURGERY

- In severe conditions
  - Plateletpheresis (removal of platelets from blood)

DYSPLASTIC & PROLIFERATIVE DISORDERS OVERVIEW

	RBC	WBC	PLATELETS
POLYCYTHEMIA VERA	↑↑ normocytic, normochromic RBCs Post-polycythemic myelofibrotic stage → leukoerythroblastic blood smear: dacrocytes, poikilocytosis, nucleated RBCs	↑ neutrophils Blasts observed as leukoerythroblastic characteristics emerge	↑ No morphological changes ↑ megakaryocytic proliferation in bone marrow
ESSENTIAL THROMBOCYTHEMIA	Normal	Normal	↑↑Anisocytosis ↑ megakaryocytes: large, hyperlobulated (staghorn-like) nuclei
MYELODYSPLASTIC SYNDROME	↓ Erythroid dysplasia: macrocytosis, multinucleation, cytoplasmic vacuoles; aniso-/poikilocytosis; ring sideroblasts	↓ Granulocytic dysplasia: hypogranularity; unilobed or bilobed pseudo-Pelger-Huët nuclei	↓ Thrombocytic dysplasia: mega-thrombocytes; altered granulation → impaired aggregation Pawn ball megakaryocytes
PRIMARY MYELOFIBROSIS	↓ Leukoerythroblastosis → dacrocytes, poikilocytosis, nucleated RBCs	↑ or ↓ Immature granulocytes; occasional pseudo–Pelger-Huët nuclei	↑ or ↓ Megathrombocytes, altered granulation → impaired aggregation Megakaryocyte hyperplasia