NON-NEOPLASTIC WHITE BLOOD CELL DISORDERS

Reactive Neutrophilia
Increase of neutrophils in response to inflammation. Causes include infection (bacteria), inflammatory and immunologic disorders, trauma, and medication such as steroids

**Blood morphology:** Neutrophils show “toxic” changes: toxic granules (heavy cytoplasmic granules), cytoplasmic vacuoles, Dohle bodies

- Left-shift: presence of immature granulocytes, mostly bands, may also have metamyelocytes and myelocytes

**Bone marrow morphology:** Hypercellularity with myeloid hyperplasia

**Blood work:**
- LAP score: high

**Differential diagnosis:** *Chronic myeloid leukemia:* Basophilia, may have blasts, *BCR-ABL1*+, LAP score low

*Chronic neutrophilic leukemia:* Mostly segmented neutrophils, *CSF3R* mutation

MYH9-Related Disorders (May-Hegglin Anomaly and related disorders)
Autosomal dominant giant platelet disorders, caused by mutations in the *MYH9* gene.

- Includes May-Hegglin, Fletcher, Sebastian, Epstein syndromes
- Triad of thrombocytopenia, giant platelets, inclusion bodies in leukocytes
- Asymptomatic in most patients, others have mild bleeding tendency
- Variable clinical presentation with ocular, ear, neurologic abnormalities

**Blood morphology:** Large blue cytoplasmic inclusions resemble Dohle body. The inclusions are larger than true Dohle bodies and represent paracrystalline array of ribosomes

- Inclusions present in neutrophils, eosinophils, basophils, and monocytes
- Large platelets

**Bone marrow morphology:** Not indicated

**Blood work:** *MYH9* mutation analysis

**Differential diagnosis:** Other diseases with thrombocytopenia such as ITP

Alder-Reilly Anomaly
A group of autosomal recessive, inherited white blood cell diseases associated with mucopolysaccharidosis, lipofuscinosis, and Tay-Sachs disease

- Accumulation of partially-degraded mucopolysaccharides in neutrophil lysosomes.
- Neutrophil function not affected

**Blood morphology:** Numerous abnormal coarse azurophilic granules in cytoplasm of granulocytes and variably in monocytes

**Bone marrow morphology:** Not indicated

**Blood work:** Blood smear review

**Differential diagnosis:** Toxic granules in reactive neutrophilia
**Chediak-Higashi Syndrome**

An autosomal recessive disorder in children, characterized by recurrent infection (abnormal granulocytic function), oculocutaneous albinism (abnormal melanosomes), bleeding tendency, and multiple neurologic abnormalities.

Caused by mutations in *CHS1* gene, which functions in lysosomal trafficking.

Abnormal endosomal-lysosomal fusion results in abnormal cytoplasmic granules

**Increased risk of lymphoid malignancy**

**Blood morphology:** Large abnormal cytoplasmic granules in granulocytes, monocytes, and lymphocytes

**Bone marrow morphology:** Not indicated

**Blood work:** *CHS1* mutation analysis

**Differential diagnosis:** Toxic granules in reactive neutrophilia

---

**Infectious Mononucleosis (IM)**

Reactive lymphocytosis caused by acute EBV infection

Route of infection through oral nasal

Children and young adults most common, pharyngitis, cervical lymphadenopathy

**Blood morphology:** Increased large reactive lymphocytes known as “Downey cells”. Cells have large mature nuclei and increased pale cytoplasm without granules. The cytoplasm often has “skirting” morphology. These cells are cytotoxic T cells (CD8+) in response to EBV infected B cells

**Bone marrow morphology:** Nonspecific, not indicated

**Lymph node morphology:** Primarily affect interfollicular/paracortical region. Expanded paracortex contains variable number of large B-immunoblasts and T-immunoblasts.

**Blood work:** *Heterophile antibodies*: Detects antibodies against multiple EBV antigens VCA, EA, and EBNA

*EBV specific serologic test:* IgM: active infection, IgG: past infection. Most adults carry IgG

*Quantitative serum EBV titer:* by PCR

**Differential diagnosis:** Infectious mononucleosis-like syndrome: acute CMV infection. Clinical and blood findings similar to IM. Heterophile antibody negative, serum anti CMV-antibody positive

**Treatment:** Self limited

---

**Large Granular Lymphocytosis (Reactive)**

Reactive lymphocytosis caused by increase of large granular lymphocytes

Often coexisting with neutropenia and autoimmune diseases

Associated with a broad spectrum of clinical conditions: rheumatoid arthritis (RA) and other autoimmune diseases, Felty’s syndrome (neutropenia, splenomegaly, RA), viral infection (HIV etc), post chemotherapy and bone marrow transplant

**Blood morphology:** Increased large granular lymphocytes: small to medium sized, mature nuclei, no nucleoli, abundant pale blue cytoplasm with variable number of azurophilic granules. Often associated with neutropenia

**Bone marrow morphology:** No significant increase of LGL in bone marrow (better seen by CD3 stain). Must be differentiated from LGL leukemia (more prominent infiltrate, linear pattern)

**Blood work:** *Flow cytometry:* Increased T-LGL (CD3+, CD57+) or NK-LGL (CD3-, CD56+), or most commonly both. Some LGL can coexpress CD57 and CD56. Negative clonality by KIR (killer IG-like receptor) isoforms

**Molecular study:** T-cell gene rearrangement (TCR) usually negative. Some LGL can be positive for TCR, which in isolation is not diagnostic for leukemia
Differential diagnosis: LGL leukemia of T-cell type or NK-cell type
Treatment: Usually self-limited. In patients with underlying disease (such as RA), may persist for long time