Hematopoiesis and Benign Blood Cell Disorders — Symptoms and Treatment

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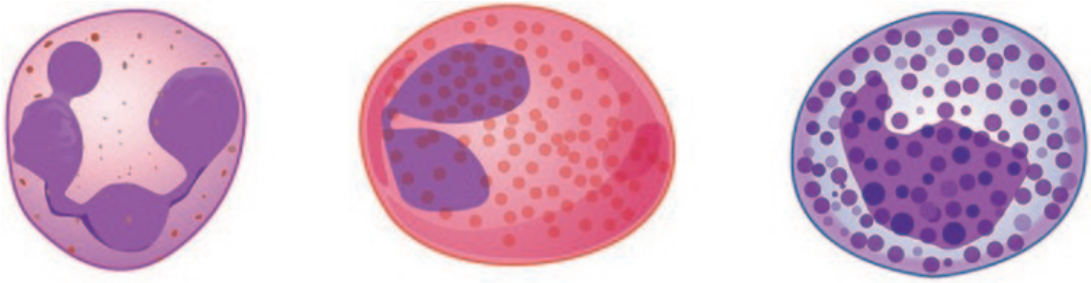
Hematopoiesis is the process of blood cell formation. It begins in embryogenesis and progresses to adulthood to replenish the cellular component of blood. The sites of hematopoiesis include the yolk sac at the embryological age of 0 - 2 months and the liver and spleen during the embryological age of 2 - 7 months. The bone marrow and thymus are definitive sites of hematopoiesis that take over the function from 8 months to adulthood. Extramedullary hematopoiesis in the spleen and liver can either the bone marrow is destroyed and cannot fulfill the function anymore.



Overview of Hematopoiesis

Hematopoiesis begins with a pluripotential stem cell in the bone marrow which can either reproduce itself or differentiate into more specific cells. **The pluripotent stem cells resemble a small/medium sized lymphocyte** that is CD34+ or CD38+ on immunological testing.

For a pluripotent stem cell to produce blood cells, it must take the pathway of differentiation into more specific cells. This begins with the formation of hematopoietic progenitor cells which, unlike the pluripotent cells, have a limited potential to develop into various cells i.e. they could either be lymphoid lineage progenitors or myeloid lineage progenitors. They also lack self-renewal properties.

The common lymphoid progenitor cells undergo **various differentiation processes to form B lymphocytes, T lymphocytes or natural killer cells,** while the common myeloid progenitor cells undergo further differentiation to form granulocytes, erythrocytes, macrophages, and megakaryocytes. After the cells are produced from the hematopoietic sites, they are then released into circulation to carry out their various functions.

Differentiation

1. Erythrocytes that carry oxygen and nutrients into the blood to peripheral organs. They also remove waste products from these organs.
2. Lymphocyte cells which are tasked with fighting infections and protect the body.
3. Myelocytic cells that include:
   Granulocytes and macrophages that also boost the body's immunity.
   Megakaryocytes that help in the coagulation of blood to avoid bleeding.

Groups of blood cell disorders

- Malignant disorders of blood
- Benign disorders of blood
- Red blood cell disorders
- Anemia
- Erythrocytosis
- Disorders of lymphocyte cells
- Lymphocytosis
- Lymphopenia
- Disorders of myelocytic cells
- Leukocytosis
- Monocytic leukocytosis
- Eosinophilic leukocytosis
- Basophilic leukocytosis
- Neutrophilic leukocytosis
- Granulocytopenia/agranulocytosis/neutropenia

Lymphocytosis

Lymphocytosis is an increase in the number of white blood cells in peripheral circulation to a level higher than 4.0 x109/L.
The condition is a common finding, especially in infectious processes that produce a neutrophilic reaction.

Etiology

Common causes of lymphocytosis include:

- Glandular fever that is characterized by fever, sore throat, lymphadenopathy, and abnormal lymphocytes. This state is seen in viral infections such as Epstein Barr virus, Cytomegalovirus, and Human immunodeficiency virus.
- Chronic infections such as herpes simplex, hepatitis, and toxoplasmosis or chronic infections such as tuberculosis and brucellosis.
- Chronic lymphoid leukemias.
- Acute lymphoblastic leukemias.
- Non-Hodgkin's lymphoma.
- Thyrotoxicosis.
- Infectious mononucleosis is a rise in lymphocyte count that arises from primary Epstein Barr virus infection leading to suppression of B lymphocytes and a clonal T cell expansion and lymphocytosis. It is marked by heterophile antibodies that react with sheep and horse antibodies.

Epidemiology

Lymphocytosis is more common in the ages of 15 – 45 years. It is mainly associated with infectious processes.

Presentation

The condition presents with a **Prodromal phase that mainly has lethargy, general body malaise, headache, stiff neck, and cough**. Established disease which presents with Lymphadenopathy which mainly affects the cervical region bilaterally. However, 50% of patients have generalized lymphadenopathy. The palpable lymph nodes may be tender and discrete. It also presents with inflamed oral or pharyngeal mucosal membranes, fever, morbilliform rash, headache, photophobia, and periorbital edema.

Other forms are:

- Hepatosplenomegaly
- Purpura
- Peripheral neuropathy
- Anemia

Investigations

CBC

A **complete blood count (CBC) indicates a white blood cell count that is greater than 4.0×109/L**. May also show mild leukocytosis.

PBF

Peripheral blood film (PBF) shows atypical lymphocytes that may possess abnormal morphology or granules within the cytoplasm.

Serum heterophilic antibodies

Serum heterophilic antibodies are present as seen in Paul-Burnell test.
Other markers of infection such as EBV antibodies, HIV DNA-PCR may be sought in other tests to identify the cause of lymphocytosis.

Differential diagnosis

Acute and chronic leukemias which present with alterations in other cell lines. They are malignant blood cell disorders thus present with a more aggressive clinical picture of bleeding, infections, and wasting. Infections that may cause lymphocytoses such as Toxoplasmosis and tuberculosis should be ruled out.

Treatment

Symptomatic treatment focuses on the comfort of the patient by the administration of antipyretics to control fevers and nutritional support for the wasted patients.

In severe infections, or elevations of the lymphocyte count, immunosuppression with corticosteroid therapy is considered.

Leukocytosis

Leukocytosis is an **increase in the number of white blood cells in peripheral circulation due to any cause**. A white blood cell count of greater than 8.5×103/mm3 is considered abnormal.

The condition is a common finding, especially in infectious processes that produce a neutrophilic reaction.

Classification

Leukocytosis may be **classified based on the type of cells** that are affected into:

Neutrophilia, eosinophilia/ eosinophilic leukocytosis, basophilia/ basophilic leukocytosis and monocytosis. The conditions may occur singly or in combination.

Common causes of neutrophilia

- Bacterial infections with pyogenic bacteria
- Inflammation/tissue necrosis such as seen in myositis and vasculitis
- Metabolic disorders such as uremic acidosis and gout
- Neoplastic processes such as lymphoma and melanoma
- Drugs such as lithium and steroids
- Myeloproliferative diseases
- Asplenia

Causes of eosinophilic leukocytosis

- Allergic reactions such as bronchial asthma, hay fever and urticaria
- Parasitic infections such as amoebiasis, hookworm, ascariasis, and schistosomiasis
- Skin diseases such as pemphigus and psoriasis
- Drug sensitivity
- Polyarteritis nodusa
- Hodgkin’s disease
- Metastatic malignancy
- Hypereosinophilic syndrome

Causes of monocytosis

- Chronic bacterial infections such as Tuberculosis and Brucella
- Connective tissue diseases such as systemic lupus erythematosus
- Chronic neutropenia
- Hodgkin’s disease
- Malignancies such as Acute myelogenous leukemia

Epidemiology

Leukocytosis is one of the most commonly observed blood changes. It is readily seen in acutely ill patients and **in response to a variety of infections, hemorrhage, cancer processes or drug exposure**. It is seen in up to 33% of patients with upper gastrointestinal bleeding.

Presentation

- Fever due to release of leucocyte pyrogens in excessive amounts
- Bleeding/easy bruisability due to depression of other cell lines in most conditions
- General body malaise
- Peripheral neuropathy
- Poor appetite and loss of weight
- Difficulty in breathing or seeing

Investigations

Complete blood count (CBC) indicates an elevated white blood cell count. Peripheral blood film (PBF) shows a shift to the left with band forms such as metamyelocytes identified in circulation. Abnormal morphologies of white blood cells such as toxic granulations and docile bodies may be seen. Elevated neutrophil alkaline phosphatase (NAP) score of greater than 100.

Differential diagnosis

Malignant blood disorders, such as lymphoproliferative diseases, must be ruled out since they present with leukocytosis as part of the symptomatology, so do lymphoma, infectious processes such as viral infection with tuberculosis and viral infection, and drug induced toxicities.

Treatment

Steroids are administered to lower the amount of inflammation and provide symptomatic relief.
Control of fevers, pain and malaise with supportive therapy has been encouraged. **IV fluids and electrolyte supplementation to correct deficits in tumor lysis syndrome** are also common.

Leukapheresis to separate the blood cells from the fluid part of blood and reduce the number of white blood cells.

Prognosis

Leukocytosis is associated with high mortality and morbidity for patients with hyperleukocytosis and resulting tumor lysis syndrome due to a breakdown of the cells in the body.

Neutropenia (Agranulocytosis)

Neutropenia is a condition that is **characterized by a neutrophil count of less than 2.5x 109/L or absolute count of 2500**. Any fall below 0.5×109/L or an absolute count of less than 500 indicates severe neutropenia and that the patient is susceptible to all forms of infections.

Etiology

Common causes of neutropenia

- Chemotherapy such as methotrexate use.
- Acute and chronic leukemia.
- Kostmann's syndrome which is a rare congenital disease that is characterized by a low neutrophil count and an increase risk of infection since childhood. Mainly presents at 1 year.
- Myelokathexis – a rare neutrophil disorder where the neutrophil function is compromised.
- Myelofibrosis.
- Myelodysplastic syndromes.
- Chronic alcohol abuse.
- Vitamin deficiency.
- Hepatitis A, B, and other viral infections.
- Rheumatoid arthritis.
- Antibiotic use such as chloramphenicol.
- Hypersplenism where there is an abnormally high level of neutrophil destruction in the spleen.
- Autoimmune conditions such as Systemic lupus erythematosus and Felty syndrome.
- Drug induced neutropenia as seen with phenothiazines use.

Epidemiology

Neutropenia may occur alone or in the setting of pancytopenia. **It affects 1.0 – 3.4 million people with the elderly population being more affected.** It is more common among females, and drug-induced neutropenia is a common form which may take the dose-dependent or idiosyncratic drug reaction.

Pathophysiology

Neutropenia may arise from any of the three pathogenic pathways:

1. Insufficient bone marrow production as seen in the destruction of the bone marrow and infiltration of the bone marrow by infection.
2. Shifts of the neutrophils from the circulating pool of cells.
3. Increased destruction of the circulating pool of neutrophils. The neutrophilic injury may arise from immunological disorders such as systemic lupus erythematosus, drug toxicities, and splenic sequestration.

Presentation

The condition presents with:

- Recurrent mucosal infections more so in the mouth, throat, and skin due to low immunity
- Septicemia
- Fever, chills, and prostration
- Stomatitis and periodontitis
- Splenomegaly
- Petechial bleeds and easy bruisability due to depression or other cell lines in most conditions
- Growth retardation
- Fever and general body malaise
- Poor appetite and loss of weight

Investigations

A complete blood count (CBC) indicates a low neutrophil count in the peripheral circulation.
Bone marrow aspirate and biopsy (BMA) shows the presence of multiple precursors in myelodysplasia and infiltration. There may be a hypercellular marrow indicating peripheral destruction, or a hypocellular marrow indicating marrow infiltration and bone marrow failure.
Further workups for identification of a focus of infection such as cultures, urinalysis, sputum, and stool examinations.

Differential diagnosis

- Leukemias, such as Acute myelogenous leukemia
- Sepsis that may depress all cell lines
- Aplastic anemia
- Lymphoma

Treatment

Stop offending drugs, if any. Treat any infections with **antibiotics, antifungals, and antiviral agents**. Prophylactic agents if the infective process is not yet identified. Administer hemopoietic growth factors, such as G-CSF to replenish the level of neutrophils. Steroid therapy where autoimmune causes have been identified. Splenectomy to avoid overt neutrophil destruction.

Prognosis

It depends on the etiology severity and presence of comorbidities. The **survival of these patients depends on the effectiveness of infection control** that can be achieved by broad-spectrum antibiotic coverage and replenishment of neutrophils. Mortality is mainly due to severe infections that mostly arise during periods of severe neutropenia.

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Notes