Session 5
Lymphatic and Haematological Disorders 3
Bioscience Department
Session Learning Outcomes

At the end of the session, you should be able to

- Define and discuss the causes, clinical features, pathophysiology and management of Aplastic Anaemia.
- Define and classify various types of haematological malignancies including various types of Leukaemia and Lymphomas.
- Explain the pathophysiology, clinical features, classifications and management of different types of acute and chronic leukaemia.
- Discuss the clinical features, investigations, and management of Paraproteinaemias - Multiple Myeloma.
Session Plan

- Aplastic anaemia
- Haematological malignancies
  - Leukaemias
    - Acute Lymphoblastic and Myeloid Leukaemia
    - Chronic Lymphoblastic and Myeloid Leukaemia
  - Lymphomas
    - Hodgkin’s Lymphoma
    - Non Hodgkin's Lymphoma
  - Paraproteinaemia
    - Monoclonal gammopathy of uncertain significance (MGUS)
    - Waldenstrom’s macroglobulinaemia
    - Multiple myeloma
Aplastic Anaemia
Aplastic Anaemia

Definition: A disorder of pluripotential bone marrow stem cells that results in Pancytopenia.

- **Aetiology:**
  - Inherited defects (Rare)
    - Fanconi’s anaemia
    - Dyskeratosis congenita
    - Amegakaryocytic thrombocytopenia

- **Acquired defects**
  - Primary idiopathic
  - Secondary:
    - Drugs
    - Chemicals
    - Radiation
    - Viral hepatitis
    - Pregnancy
    - Paroxysmal nocturnal haemoglobinuria
Aplastic Anaemia

- **Pathophysiology:**
  - Inherited/ acquired defects → stimulate cellular immune response → production of cytokines (interferon, tumor necrosis factor [TNF]) by activated T cells → cytokines suppress normal stem cell growth and development → bone marrow aplasia → Pancytopenia

- **Clinical features:**
  - Symptoms of bone marrow failure, usually anaemia or bleeding, and less commonly, infections.
Aplastic Anaemia

Diagnosis:
• Full blood count
• Peripheral blood smear
• Bone marrow examination

Management:
• Blood transfusion
• Bone marrow transplant
Aplastic Anaemia

Aplastic bone marrow

Normal bone marrow

http://quotesgram.com/bone-marrow-quotes/
Aplastic Anaemia: A pluripotential bone marrow stem cells disorder that results in bone marrow aplasia and Pancytopenia

Inherited defects: Falconi’s anaemia, Dyskaratosis congenital, Amegkaryocytic thrombocytopenia

Acquired: idiopathic, Drugs, Chemicals, Radiation, Viral hepatitis, Pregnancy, Paroxysmal nocturnal haemoglobinuria

Cellular immune response

cytokines (interferon, tumor necrosis factor [TNF]) production by activated T cells

Normal stem cell growth and development suppressed

Bone marrow aplasia

Symptoms of Thrombocytopenia: Patechia, easy bruising, bleeding from nose, gums,, stool

Symptoms of Anaemia: weakness, fatigability, and pallor, SOB, dizziness, heart murmur, cardiac enlargement, heart failure

Symptoms of neutropenia: predispositions to infections

Diagnosis:
FBC
Peripheral blood smear
Bone marrow examination

Management:
Blood transfusion
Bone marrow transplant

Diagnosis:

Clinical features | Definition | Aetiology | Pathophysiology
---|---|---|---
Complications | Management |
Leukaemias
Leukaemias

Definition: Malignant disorders of the haematopoietic stem cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and/or peripheral blood.

- Risk factors:
  - Ionising radiation
  - Cytotoxic drugs
  - Retroviruses
  - Genetic
  - Immunological
Leukaemias

○ Classification:
  • Acute lymphoblastic leukaemia, ALL (more common in children)
  • Acute myeloid leukaemia, AML (more common in elderly)
  • Chronic lymphocytic leukaemia, CLL (more common in elderly)
  • Chronic myeloid leukaemia, CML (more common in elderly)
Acute Leukaemias

Definition: Sudden, rapidly progressive, uncontrolled proliferation of primitive stem cells, leading to an accumulation of blasts, predominantly in the bone marrow, leading to bone marrow failure and spilling of blast cells into the blood stream.

Classification:

- Acute lymphoblastic leukaemia (ALL)
  - Involves lymphoid stem cells
  - Four times more common in children

- Acute myeloid leukaemia (AML)
  - Involves myeloid stem cells – particularly granulomonocytes
  - Four times more common in adults
Acute Leukaemias

° Pathophysiology:

• ALL
  Chromosomal aberrations $\rightarrow$ dysregulation of the expression and function of transcription factors required normal hematopoietic cell development $\rightarrow$ altered hematopoiesis

• AML
  Acquired genetic alterations $\rightarrow$ inhibit terminal myeloid differentiation $\rightarrow$ accumulation of relatively undifferentiated blast cells in bone marrow $\rightarrow$ suppression of the remaining progenitor cells that leads to anaemia, neutropenia, and thrombocytopenia
Acute Leukaemias

- Clinical features:
  - Fever, night sweat, weight loss, fatigue, pallor
  - Bleeding in the gums, Petechial haemorrhage
  - Enlargement of spleen and liver
  - Infiltration of lymph nodes
  - Tender bones and bone-pains esp. in children
  - Sternum tender and painful
  - Leukostasis leading to obstruction in the pulmonary and cerebral circulations.
    - Cranial nerve palsies, headache, nausea, vomiting, papilledema, occasionally seizures and coma
    - Sudden shortness of breath and progressive dyspnoea
Acute Leukaemias

- Diagnosis:
  - Full blood count
  - Peripheral blood smear
  - Bone marrow examination
  - Immunophenotyping, chromosome and molecular analysis

A. Acute myeloblastic leukaemia: There are Auer rods in the cytoplasm of the blast cells in this smear.

B. Grossman, S, Porth, CM 2013, Porth’s pathophysiology, Concepts of Altered Health States, 9th edn, Lippincott Williams & Wilkins

B. Acute lymphoblastic Leukaemia. There are irregular nuclei in the lymphoblasts in this blood smear.
Acute Leukaemias

Management:

- Specific therapy: to destroy the leukaemic clone of cells without destroying the residual normal stem cell compartment from which repopulation of the haematopoietic tissues will occur.

- Three phases:
  - Remission induction: The bulk of the tumour is destroyed by combination chemotherapy
  - Remission consolidation: If remission has been achieved, residual disease is attacked by therapy during this phase.
  - Remission maintenance. A period of maintenance therapy is given, consisting of a repeating cycle of drug administration. This may extend for up to 3 years if relapse does not occur.
Acute Leukaemias

Management:

- Supportive therapy: To deal with periods of severe bone marrow failure.
  - Red cell concentrate transfusions for Anaemia
  - Platelet transfusions for Bleeding
  - Parenteral broad-spectrum antibiotic therapy to prevent infection
  - Prophylaxis for pneumonia, Oral and pharyngeal infection, systemic fungal infection, herpes simplex
  - Treatments for metabolic problems treated accordingly if occurs
  - Psychological support
Chronic Myeloid Leukaemias

- **Definition:** a myeloproliferative stem cell disorder resulting in slow progressing proliferation of marrow granulocytes, erythroid precursors, and megakaryocytes.

- **Aetiology:**
  - Chromosome abnormality: Philadelphia (Ph) chromosome formed by reciprocal translocation t(9;22)
Chronic Myeloid Leukaemias

o Pathophysiology:
  Translocation of genes from chromosome from 9 to 22 create a new BCR ABL “fusion” gene (an oncogene) on 22 → a “fusion” protein, (tyrosine kinase) with increased phosphorylating activity → altered cellular proliferation, differentiation and survival.

o Clinical features:
  • Three phases:
    – A chronic phase of variable length
    – A short accelerated phase
    – A terminal blast crisis phase
Chronic Myeloid Leukaemias

- Clinical features: (cont.)
  - A chronic phase of variable length:
    - Slow onset with chronic phase of 3-5 years duration
    - Nonspecific symptoms such as weakness and weight loss
    - Anaemia causing easy fatigability, and exertional dyspnoea
    - Splenomegaly
    - Hepatomegaly is less common
    - Lymphadenopathy is relatively uncommon
Chronic Myeloid Leukaemias

- Clinical features: (cont.)
  - A short accelerated phase:
    - Progressive symptoms with short phase of 6 to 12 months
    - Constitutional symptoms such as low-grade fever, night sweats, bone pain, and weight loss
    - Splenomegaly often causes a feeling of abdominal fullness and discomfort
    - Bleeding and easy bruising may arise from dysfunctional platelets.
Chronic Myeloid Leukaemias

- Clinical features: (cont.)
  - A terminal blast crisis phase:
    - Evolution to acute Leukaemia
    - Constitutional symptoms become more pronounced
    - Splenomegaly may increase significantly
    - Leukemic cells infiltration into skin, lymph nodes, bones, and CNS
    - Symptoms of leukostasis with very high blast counts
Chronic Myeloid Leukaemias

- **Diagnosis:**
  - Full blood count
  - Peripheral blood smear
  - Bone marrow examination
  - Karyotype
  - RNA analysis of blood
  - Serum LDH, urate and uric acid

- **Management:**
  - Chronic phase: Imatinib, dasatinib and nilotinib (tyrosine kinase inhibitor drugs)
  - Accelerated phase and blast crisis: chemotherapy, allogeneic bone marrow transplant
Chronic Lymphocytic Leukaemias

Definition: It is a clonal malignancy of B lymphocytes characterized by uncontrolled proliferation and accumulation of mature immuno-incompetent B lymphocytes.

Clinical features:
- Often asymptomatic in the earlier stage
- Painless lymphadenopathy
- Hepatosplenomegaly
- Fever, abdominal pain, weight loss,
- Symptoms of progressive anaemia, thrombocytopenia and hypogammaglobinaemia
### Chronic Lymphocytic Leukaemias

<table>
<thead>
<tr>
<th>Clinical stage A (60% patients)</th>
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<tbody>
<tr>
<td>• No anaemia or thrombocytopenia and fewer than three areas of lymphoid enlargement</td>
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<th>Clinical stage B (30% patients)</th>
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<tr>
<td>• No anaemia or thrombocytopenia, with three or more involved areas of lymphoid enlargement</td>
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<tr>
<th>Clinical stage C (10% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anaemia and/or thrombocytopenia, regardless of the number of areas of lymphoid enlargement</td>
</tr>
</tbody>
</table>
Chronic Lymphocytic Leukaemias

- **Diagnosis:**
  - Full blood count
  - Peripheral blood smear
  - Reticulocyte count and a direct Coombs test
  - Immunophenotyping
  - Serum immunoglobulin levels
  - Bone marrow examination

This peripheral blood smear shows an absolute lymphocytosis of small “mature” lymphocytes with clumped, smudgy chromatin and scant cytoplasm. Smudge cells (near the top right) are a common finding of Chronic lymphocytic Leukaemia.

Chronic Lymphocytic Leukaemias

- **Complications:**
  - Autoimmune haemolytic anaemia
  - Thrombocytopenia
  - High grade non-Hodgkin’s lymphoma (Richter’s transformation)
  - Hairy cell Leukaemia

- **Management:**
  - Stage A: No specific treatment
  - Stages B and C: Oral chemotherapy with chlorambucil.
  - Corticosteroids
  - Blood transfusion
  - Radiotherapy
  - Splenectomy
  - Stem cell transplant
Lymphomas
Lymphomas

- Definition: A diverse group of solid tumours composed of neoplastic lymphoid cells that vary with respect to molecular features, genetics, clinical presentation, and treatment.

- Classification:
  - Hodgkin’s lymphoma
  - Non Hodgkin’s lymphoma
Hodgkin’s Lymphomas

- Definition: A specialized form of lymphoma that features the presence of an abnormal cell called a Reed-Sternberg cell.

- Aetiology:
  - Unknown
  - More common in patients from well-educated backgrounds and small families
  - Three times more likely with a past history of infectious mononucleosis but no definitive causal link to Epstein–Barr virus infection is proven
Hodgkin’s Lymphomas

○ Clinical features:
  • Fever, chills, night sweats and weight loss
  • Pruritus and intermittent fevers associated with night sweats
  • Painless enlargement of lymph nodes (mainly above diaphragm)
  • Mediastinal masses
  • Chest discomfort with cough or dyspnoea
  • Fatigue and anaemia
  • Predisposition to infections
Hodgkin’s Lymphomas

Diagnosis:
- Lymph node biopsy
- Full blood count
- Liver function test
- Serum LDH level
- Chest X-ray
- CT scan of chest, abdomen and pelvis

Classic Reed-Sternberg cell with two nuclei containing a prominent eosinophilic nucleolus

Grossman, S, Porth, CM 2013, Porth’s pathophysiology, Concepts of Altered Health States, 9th edn, Lippincott Williams & Wilkins
Hodgkin’s Lymphomas

- **Management:**
  - Early stage disease: Chemotherapy and adjunctive radiotherapy
  - Advanced-stage disease: Chemotherapy alone
  - Disease resistant to therapy: Autologous Hematopoietic stem cell transplantation (HSCT)

- **Complications:**
  - Mainly due to treatment
    - Cardiac and pulmonary toxicity,
    - Breast cancer, lung cancer
    - Secondary myelodysplasia/AML
Non-Hodgkin's Lymphomas

- **Definition:** It represents a monoclonal proliferation of lymphoid cells of B cell (70%) or T cell (30%) origin.

- **Classification:**
  - Nodular lymphoma
  - Diffused lymphoma
  - Low grade lymphoma
  - High grade lymphoma
  - T cells lymphoma
  - B cell lymphoma

- **Aetiology:**
  - Viral infections
  - *Helicobacter pylori*
  - Chromosomal translocations
  - Congenital immunodeficiency
  - Immunosuppressed patients
Non-Hodgkin's Lymphomas

Clinical features:

- Peripheral lymphadenopathy – mainly mediastinal, intra-abdominal and pelvic
- Involvement of extra-nodal sites like bone marrow, gut, thyroid, lung, skin, testis, brain and, more rarely, bone
- Weight loss, sweats, fever and itching
- Hepatosplenomegaly
- Gut obstruction, ascites, superior vena cava obstruction and spinal cord compression
Non-Hodgkin's Lymphomas

- **Diagnosis:**
  - Same investigations as Hodgkin’s lymphoma
  - Other tests:
    - Immunophenotyping
    - Cytogenetic analysis
    - Immunoglobulin determination
    - Serum uric acid
    - HIV testing


Low-grade follicular or nodular NHL

(High-grade) diffuse NHL
Non-Hodgkin’s Lymphomas

Management:

- Asymptomatic patients may not require therapy.
- Indications for treatment: Marked systemic symptoms, lymphadenopathy causing discomfort or disfigurement, bone marrow failure or compression syndromes
- Treatment options:
  - Radiotherapy
  - Chemotherapy
  - HSCT
Paraproteinaemia
Paraproteinaemias

○ **Definition:** Overproduction of one or more classes of immunoglobulin. May be monoclonal or polyclonal.

○ **Conditions:**
  - Monoclonal gammopathy of uncertain significance
  - Waldenstrom macroglobulinaemia
  - Multiple myeloma
Monoclonal gammopathy of uncertain significance

- **Definition:** A condition with the presence of the monoclonal immunoglobulin in the serum without other findings of multiple myeloma, Waldenstrom macroglobulinaemia, lymphoma or related disease.

- **Clinical features:**
  - Asymptomatic

- **Diagnosis:**
  - Routine blood count and biochemistry are normal
  - Monoclonal paraprotein is usually present in small amounts with no lytic bone lesions.
  - The bone marrow may have increased plasma cells
Waldernstrom Macroglobulinaemia

**Definition:** This is a low-grade lymphoplasmacytoid lymphoma associated with an IgM paraprotein, causing clinical features of hyperviscosity syndrome.

**Clinical features:**
- Nosebleeds, bruising, confusion and visual disturbance
- Anaemia
- Systemic symptoms
- Splenomegaly or lymphadenopathy.
Waldenstrom Macroglobulinaemia

- **Diagnosis:**
  - IgM paraprotein associated with a raised plasma viscosity
  - The bone marrow with infiltration of lymphoid cells and prominent mast cells

- **Management:**
  - Plasmapheresis to remove IgM
  - Blood transfusion
  - Chemotherapy with alkylating agents, such as chlorambucil
Multiple Myeloma

- Definition: This is a malignant proliferation of plasma cells that produce immunoglobulin of a single heavy and light chain, a monoclonal protein commonly referred to as a paraprotein. In some cases, only light chain is produced.

Multiple Myeloma

- Clinical features:
  - The main sites involved are:
    - Bones
    - Bone marrow
  - Signs and symptoms are shown in the image

Grossman, S, Porth, CM 2013, Porth's pathophysiology, Concepts of Altered Health States, 9th edn, Lippincott Williams & Wilkins
Multiple Myeloma

- **Diagnosis:**
  - Based on two of the following criteria:
    - Increased malignant plasma cells in the bone marrow
    - Serum and/or urinary M-protein
    - Skeletal lytic lesions

- **Management:**
  - *Immediate support*
  - *Chemotherapy with or without HSCT*
  - *Radiotherapy*
  - *Bisphosphonates*
Reading and Resources

- Crowley LV, 2012, *An Introduction to Human Diseases – Pathology and Pathophysiology Correlations*, 9th edn, Jones and Bartlett Learning
Reading and Resources

- Mosby’s dictionary of medicine, nursing and health professions 2013, 9th edn, Elsevier, St. Louis, MO.
- VanMeter, KC & Hubert, RJ 2014, *Gould's pathophysiology for the health professions*, 5th edn, Elsevier, St Louis, MO.
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