Objectives

- Describe the key features of normal haematopoiesis
- Compare the differences between lymphomas and leukaemias
- Understand the principles of diagnosis and classification of lymphomas
- List the main types of myeloid neoplasms
- Understand basic functional histology of the spleen and thymus
- List a few conditions specific to the spleen and thymus

Outline

I. Haematopoiesis

a. **Overview of Normal Haematopoiesis**
b. **Anatomy of the Lymphoreticular System**

II. Leukocyte Disorders

a. **Leukopenia:** *Neutropenia, Lymphopenia*
b. **Leukocytosis**
c. **Reactive lymphoid proliferation/Lymphadenitis:** *Acute non-specific lymphadenitis, Chronic non-specific lymphadenitis, Granulomatous lymphadenitis*
d. **Neoplastic Proliferations (Lymphomas):**
    i. *Overview*
    ii. *Classification*
    iii. *Diagnosis of lymphomas (morphologic, immunophenotype, genetic/molecular and clinical features)*
    iv. *Staging of lymphoma*
    v. *Selected lymphoid neoplasms (B and NK/T-cell lymphomas, plasma cell neoplasms, Hodgkin lymphoma)*
e. **Secondary Malignancies**

III. Myeloid neoplasms

a. **Definition and classification of leukaemias**
b. **Acute Myeloid Leukaemia**
c. **Myelodysplastic Syndrome**
d. **Myeloproliferative Neoplasms:** *Chronic myeloid leukaemia, Polycythaemia vera, Essential thrombocytosis, Primary myelofibrosis*

IV. Histiocytic neoplasms

a. **Langerhans Cell Histiocytosis**

V. Spleen

a. **Basic Structure and Physiology**
b. **Non-neoplastic Conditions:** *Non-specific acute splenitis, Congestive splenomegaly, Splenic infarct, Congenital anomalies, Rupture*
c. **Neoplasms**

VI. Thymus

a. **Basic Structure and Physiology**
b. **Non-neoplastic Conditions:** *Developmental disorders, Thymic hyperplasia*
c. **Thymoma and Thymic Carcinoma**
d. **Other Thymic Neoplasms**

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed.

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. HAEMATOPOIESIS

A. Overview of Normal Haematopoiesis

- **Haematopoiesis** = formation of blood cell components (red blood cells, granulocytes, monocytes, lymphocytes and platelets) from hematopoietic stem cells (HSCs)
    - Main sites: liver (until before birth), bone marrow (4th month of gestation onwards; first throughout entire skeleton, then axial skeleton only after puberty)
    - 3 main haematopoietic cell lines in the bone marrow: erythroid series (erythrocytes – RBCs), granulocytic series (polymorphs – WBCs), megakaryocytic series (platelets)
    - Response to short-term physiologic needs regulated by haematopoietic growth factors, with feedback loops to allow only the appropriate numbers of formed blood elements (RBC, WBC and platelets) to be created and maintained
- **HSCs** = pluripotent cells that give rise to several types of early progenitor cells with more restricted differentiation potential, which further give rise to even more committed progenitors and subsequently, precursors such as myeloblasts, proerythroblasts and megakaryoblasts that are the immediate progenitors of mature granulocytes, red blood cells and platelets. To be able to maintain haematopoiesis, HSCs also need to be capable of self-renewal
- **Diseases that affect blood cell production**: Infections, inflammation, genetic defects, toxins, nutritional deficiencies, tumours. Primary tumours of haematopoietic origin often harbour mutations that block progenitor cell maturation or bypass their dependence on growth factors, leading to their unregulated clonal expansion that can replace the normal marrow progenitors and spread to other haematopoietic organs
- You will find 2 helpful videos here, familiarising you with different types of leukocytes: https://medicine.nus.edu.sg/pathweb/pathology-demystified/haematolymphoid-system-lymph-nodes/
    - **Introduction to Leukocytes**
    - **Leukocytes in Action** (A case of acute appendicitis with special focus on the types of leukocytes)

B. Anatomy of the lymphoreticular system

Two major functional regions:

- **Primary immune organs**: Sites of initial maturation to form immune competent cells
    - **Bone marrow**: B cells, NK cells
    - **Thymus**: T cells
- **Secondary immune organs**: Sites of antigen driven replication and differentiation into committed effector cells
    - **Lymph nodes**
    - **Spleen**
    - **Mucosal associated lymphoid tissues (MALT)** e.g. mucosal lining of respiratory and GI tract
- **Tertiary lymphoid structures:** Other non-lymphoid tissues that may develop organised aggregates of immune cells with pathological stimulation

Lymph node architecture

- Organised to detect and react to antigenic stimuli in the lymph fluid

- Main regions:
    - **Cortex**: Outer / subcapsular portion with the largest number of primary and secondary B cell follicles. Primary follicles have no germinal centres, while secondary follicles arise from primary follicles that have developed germinal centres after antigenic stimulation, surrounded by mantle and marginal zones
    - **Medulla**: Portion closest to the hilum, containing medullary cords (mixture of small B and T cells, plasma cells), sinuses and vessels but minimal follicles. Sinuses carry lymph from the afferent to efferent lymphatics; the sinuses start off subcapsular and then becomes medullary as they approach the lymph node hilum
    - **Paracortex**: Tissue between the cortex and medulla, containing predominantly mature T cells, scattered B cell immunoblasts, dendritic cells, histiocytes and high endothelial venules

II. LEUKOCYTE DISORDERS

Disorders of white blood cells can be classified into deficiency of leukocytes (**leukopaenia**) or increased numbers of leukocytes (**leukocytosis**), which can be reactive or neoplastic. **Lymphadenitis** refers to the enlargement of lymph nodes due to inflammation or infection.

A. Leukopaenia

Neutropenia = reduced numbers of neutrophils (more common)

- **Causes**:
    1. **Insufficient or ineffective granulopoiesis**:
        - Disorders that suppress HSCs or committed granulocytic precursors e.g. most commonly drugs; others include aplastic anaemia and infiltrative bone marrow disorders
        - Disorders that result in defective precursors that die in the bone marrow or do not mature and do not develop into healthy blood cells e.g. myelodysplastic syndromes
    2. **Increased destruction or peripheral sequestration of neutrophils**:
        - Immunologic disorders or drugs that injure neutrophils e.g. SLE
        - Splenomegaly: usually associated with thrombocytopenia +/- anaemia
        - Increased peripheral utilisation of neutrophils: e.g. in extensive infections
- **Consequences**: High risk of infections which are often fulminant in extremely low neutrophil counts / agranulocytosis

Lymphopenia = reduced lymphocyte numbers (less common)

- **Causes**: congenital immunodeficiencies, advanced HIV infection, treatment with glucocorticoids or cytotoxic drugs, autoimmune disorders, malnutrition or certain acute viral infections (this is mainly due to sequestration of lymphocytes from the peripheral blood into lymph nodes or adherent to blood vessel walls)

B. Leukocytosis

- Growth factors that preferentially stimulate specific types of leukocytes are differentially produced in response to pathogenic stimuli, resulting in increased numbers of different leukocytes (neutrophilia, eosinophilia, basophilia,

monocytosis and lymphocytosis) in different clinical settings e.g. neutrophilic leukocytosis tends to occur in acute bacterial infections, while eosinophilia tends to be seen in allergic disorders

- **Mechanisms and causes of neutrophilic leukocytosis**:
    - **Increased marrow production (growth factor dependent)**: Chronic infection / inflammation or paraneoplastic syndromes
    - **Increased release from marrow stores into circulation**: Acute or chronic inflammation
    - **Decreased margination within vessels**: Exercise, catecholamines
    - **Decreased extravasation from blood into tissues**: Glucocorticoids

C. Reactive lymphoid proliferation (Lymphadenitis)

Lymphadenitis = regional or systemic immune reactions within lymph nodes. Can be caused by infections or inflammatory stimuli, including drugs, autoimmune conditions or unknown aetiology (Kikuchi necrotizing lymphadenitis)

Acute non-specific lymphadenitis

- Swollen painful lymph nodes; may be fluctuant if abscess forms and produce draining sinuses to the skin surface
- Due to infection or inflammation in the drainage region e.g. tonsillitis leads to cervical lymphadenopathy; systemic viral infections often result in acute generalised lymphadenopathy
- **Histology**: Large reactive germinal centres and macrophages containing debris from dead bacteria or necrotic cells. If the cause is a pyogenic organism, the lymph nodes may contain many neutrophils with suppurative necrosis

Chronic non-specific lymphadenitis

- Usually non-tender due to slow enlargement and absence of acute inflammation
- Due to a wide variety of chronic immunological stimuli esp. in axillary and inguinal lymph nodes which drain a large surface area
- May be accompanied by formation of tertiary lymphoid organs i.e. organised collections of immune cells in non-lymphoid tissues e.g. B cell follicles in inflamed synovium in rheumatoid arthritis
- **Histology**:
    - **Follicular hyperplasia**: Due to stimuli that activate humoral immune responses e.g. rheumatoid arthritis, toxoplasmosis
        - Secondary follicles of varying shapes and sizes, comprising large germinal centres with tingible-body macrophages (containing phagocytosed apoptotic debris), surrounded by mantle zone cells
        - Lymph node architecture (interfollicular T-cell zones, sinusoids) preserved
    - **Paracortical hyperplasia**: Due to stimuli that activate T-cell mediated immune response e.g. acute viral infections
        - Expanded T cell zones that encroach on the B-cell follicles and contain immunoblasts (activated T cells)
    - **Sinus histiocytosis**: Usually seen in lymph nodes draining cancers e.g. breast cancer
        - Expansion of the sinuses by macrophages, and accompanied by increased number and size of the lining endothelial cells of the sinusoids

Granulomatous lymphadenitis

- Lymph node involved by granulomas, which can be due to infectious (e.g. mycobacterial, fungal, cat-scratch disease, certain bacteria) or non-infectious (e.g. sarcoidosis, drugs, autoimmune conditions, lymphomas, foreign bodies) causes

D. Neoplastic proliferations (Lymphomas)

Overview

- Lymphoid neoplasms include tumours of B-cell, T-cell and NK-cell origin. Myeloid neoplasms arise from early haematopoietic progenitors and are covered in the following section (*III. Myeloid Neoplasms*)
- Development of lymphoid neoplasms involves genetic alterations, infections +/- background of chronic inflammation and environmental risk factors
    - **Genetic alterations**: Chromosomal translocations and other abnormalities are seen in the majority of lymphoid neoplasms, have specific associations and are important in their pathogenesis. The genes involved are often critical to the development, growth or survival of the normal white blood cell. The oncoproteins often block normal maturation / differentiation, activate pro-growth signaling pathways, increase self-renewal and/or prevent cell death, thus giving them stem cell-like properties. Some of these errors occur during attempted antigen receptor gene diversification in germinal centre B-cells and precursor B and T cells
    - **Inherited genetic factors**: Genetic diseases that promote genomic instability e.g. Fanconi anaemia are at increased risk of acute leukaemia
    - **Viruses**: EBV, HTLV-1, HBV and HHV8 are associated with certain lymphomas
    - **Chronic inflammation**: In localised chronic inflammation, the lymphoid neoplasm almost always arises in the inflamed tissue e.g. gastric B-cell lymphomas in *H.pylori* infections
    - **Iatrogenic factors and smoking**: The mutagenic effects of ionising radiation, chemotherapeutic drugs and carcinogens in smoking increase the risk of developing lymphoid and myeloid neoplasms

Classification of lymphoid neoplasms

- **Lymphoma** = neoplastic proliferation of lymphoid cells that usually present as discrete tissue masses outside the bone marrow at sites of normal lymphoid homing e.g. in lymph nodes, spleen, thymus, but can spread to bone marrow
    - Patients frequently present with enlarged lymph nodes / immune organs, symptoms related to extranodal site involvement (e.g. obstruction of hollow viscera or interference of the normal function of solid organs) or systemic symptoms from release of cytokines (fever, night sweats, weight loss)
    - Can be divided into **Hodgkin lymphomas** and **non-Hodgkin lymphomas** (B or T/NK cell neoplasms, depending on cell lineage), based on cell or origin and their distinctive pathologic features.
        - Non-Hodgkin lymphomas (NHL): Includes B-cell and T/NK-cell lymphomas and forms the majority of lymphomas. B-cell lymphomas are more common than T/NK-cell lymphomas.
        - Hodgkin lymphomas (HL) show some differences compared to NHL in that they favour axial (e.g. cervical, mediastinal, para-aortic) nodes; spread by anatomically contiguous nodal sites and only very rarely occur in extranodal sites, in contrast to NHL.
    - Can also be subdivided into **aggressive** and **indolent**, based on clinical behaviour:

    - **Aggressive lymphomas**: Characterised by high proliferation (defective cell cycle control) and thus have a shorter natural history (in absence of therapy) and more often localised at presentation. With appropriate aggressive therapy, disease can be curable
    - **Indolent lymphomas**: Characterised by low proliferation (defective apoptosis) and thus have a prolonged natural history and widespread at diagnosis. Mostly incurable unless localised disease or marrow ablation with stem cell transplant
- **Plasma cell neoplasms** often arise in the bone marrow with infrequent involvement of both the lymph nodes or peripheral blood. They can present with pathologic fractures or symptoms related to the immunoglobulins produced
- There can be overlap in presentations and during disease evolution of lymphomas and leukaemias. E.g. Lymphomas can disseminate into bone marrow and some leukaemias (less commonly) may arise as soft tissue masses without bone marrow involvement at first presentation.

Diagnosis of lymphomas

- Most lymphoid neoplasms originate from a recognisable stage of B- or T- cell differentiation, which helps in their classification. The neoplastic B and T cells also tend to recapitulate the behaviour of their normal cellular counterparts, leading to characteristic patterns of involvement e.g. follicular lymphomas home to germinal centres in lymph nodes
- Specific classification and diagnosis of lymphoid neoplasms requires a combination of **morphologic**, **immunophenotypic**, **genetic/molecular** and **clinical features:**
    - **Clinical features**: Nodal vs extranodal, primary site of disease, any immune deficiency or infections, peripheral blood counts (for leukaemia)
    - **Morphology**: Disrupted normal lymph node architecture, diffuse vs nodular growth pattern, size of the neoplastic lymphoid cells, specific morphologic features
    - **Immunophenotype**: Detects specific surface antigens of the lymphoid cells that can indicate cell lineage (B vs T) or are characteristic of specific subtypes or molecular abnormalities
    - **Genetic/molecular features**: Certain DNA alterations are characteristic of specific subtypes
- **Molecular assessment**
    - **Clonality** testing through analysis of antigen receptor genes and their protein products can distinguish between reactive (polyclonal) and neoplastic (monoclonal) lymphoid proliferations. This is as transformation of lymphoid cells generally occurs before antigen receptor gene rearrangement, meaning all daughter cells derived from the transformed neoplastic cell will share the same antigen receptor gene configuration and therefore have identical antigen receptor proteins, compared to reactive immune responses which generate many different antigen receptors
    - **Testing for DNA alterations:** Fluorescence in situ hybridization (FISH) or chromosome karyotyping can detect characteristic translocations in certain lymphomas e.g. BCL2 translocation in follicular lymphoma and MYC translocation in Burkitt lymphoma.

Staging of lymphoma

- Defines extent of disease
- Ann Arbor system is commonly used (based on number and location of nodal regions in relation to the diaphragm, and presence of extralymphatic organ involvement)

- Hodgkin lymphoma spreads in a predictable fashion (to anatomically contiguous lymphoid tissues via lymphatics). In contrast, most forms of non-Hodgkin lymphoma show non-contiguous spread to multiple peripheral lymph nodes and frequent extranodal presentation
- For HL:
    - Staging is most useful to guide therapy in Hodgkin lymphoma
    - Tumour stage rather than histologic subtype of HL is the most important prognostic variable
    - Low stage disease can be cured by localised radiotherapy, while higher stage disease with B symptoms require chemotherapy +/- radiotherapy

Selected more common lymphoid neoplasms

Diagnosis	Genotype	Key clinical and morphologic features
Non-Hodgkin lymphomas (NHL)		
A) Neoplasms of immature B and T cells		
B-cell acute lymphoblastic leukaemia/lymphoma *most common cancer in children	Diverse chromosomal translocations, including t(12;21) *ETV6-RUNX1*	• Aggressive • Mostly children • Presents as leukaemia with symptoms related to bone marrow replacement e.g. pancytopenia and mass effects from neoplastic infiltration e.g. splenomegaly
T-cell acute lymphoblastic leukaemia/lymphoma	Diverse chromosomal translocations; *NOTCH1* mutations	• Aggressive • Usually adolescent males • P/w thymic mass +/- bone marrow involvement
B) Neoplasms of mature B cells (majority of lymphoid neoplasms)		
Burkitt lymphoma	Translocations involving *MYC* and *Ig*, usually t(8;14);	• Very aggressive; 70-80% children curable (adults variable) • Adolescents / young adults • P/w extranodal masses; 3 subtypes with identical histology but different clinical and virologic characteristics: (1) Endemic (Africa): children, jaw, EBV+ (2) Sporadic (Western countries): children/young adults, ileocaecal region (3) Immunodeficiency-related: HIV+ • **Pathogenesis**: t(8;14) leads to upregulation of *MYC* oncogene, a cell cycle regulation gene • **Histology**: Diffuse infiltration of lymph node by intermediate-sized lymphoid cells with a high mitotic rate and numerous apoptotic cells phagocytosed by macrophages, imparting a "starry-sky appearance" • **Immunophenotype**: CD20+ (B-cell markers), CD10+ (follicle centre marker)
Diffuse large B cell lymphoma *most common NHL in adults	Diverse chromosomal translocations, including *BCL6*, *BCL2* or *MYC*	• Aggressive; 60% curable with aggressive chemotherapy • Usually older adults but also children • P/w rapidly growing mass, can be extranodal • **Histology**: Diffuse infiltration of lymph node, comprising large lymphoid cells • **Immunophenotype**: CD20+ (B-cell markers)
Follicular lymphoma *2nd most common NHL in adults	t(14;18) *BCL2-IGH*	• Indolent; usually incurable with waxing-waning course • Older adults • P/w painless generalised lymphadenopathy +/- marrow involvement • **Pathogenesis**: t(14;18) leads to overexpression of anti-apoptotic protein Bcl2, promoting survival

		• **Histology**: Nodular or nodular and diffuse growth pattern in involved lymph nodes, comprising a mixture of centrocytes (small cleaved lymphocytes) and centroblasts (larger lymphoid cells with several nucleoli) • **Immunophenotype**: CD20+ (B-cell marker), CD10+ (follicle centre marker), Bcl2+
Plasma cell neoplasms	Diverse rearrangements involving *IGH*; 13q del	Plasmacytoma • Indolent • Isolated mass in bone or soft tissue Multiple myeloma • Moderately aggressive • Older adults with destructive lytic bone lesions (usually axial skeleton), pathologic fractures, hypercalcemia, renal failure • Neoplastic plasma cells suppress normal humoral immunity
C) Neoplasms of mature T cells or NK cells		
Angioimmunoblastic T-cell lymphoma	Mutations of *TET2*, *DNMT3A*, *RHOA*	• Common T-cell lymphoma • Adults, presents with generalized lymphadenopathy, skin rash • Neoplastic T cells show T-follicular helper signature • Prognosis usually dismal
Extranodal NK/T cell lymphoma	Deletion of 6q	• Highly aggressive; EBV-associated • Responds well to radiotherapy and immune checkpoint inhibitors but not the conventional chemotherapy • Adults; more common in Asia but rare in US/Europe • P/w destructive extranodal masses, commonly nasopharyngeal
Hodgkin lymphoma		
Classic Hodgkin lymphoma *Subtypes include nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte depletion*	Diverse chromosomal abnormalities;	• Bimodal age incidence (late adolescence/young adulthood; 6th decade) • Subset are EBV-associated • P/w painless lymphadenopathy +/- constitutional symptoms (B symptoms) of fever, night sweats, weight loss • **Histology**: Neoplastic Reed-Sternberg (RS) cells (large cells with multiple nuclei or single multilobate nucleus with large nucleoli) in a non-neoplastic inflammatory background including lymphocytes, histiocytes, eosinophils and plasma cells • **RS cells are derived from** B-cells which has downregulated B-cell program, hence some B cell markers are not expressed. **Immunophenotype**: PAX5+ but CD20- (altered B cell) CD30+, CD15+ • Curable in most cases by radiation +/- chemotherapy

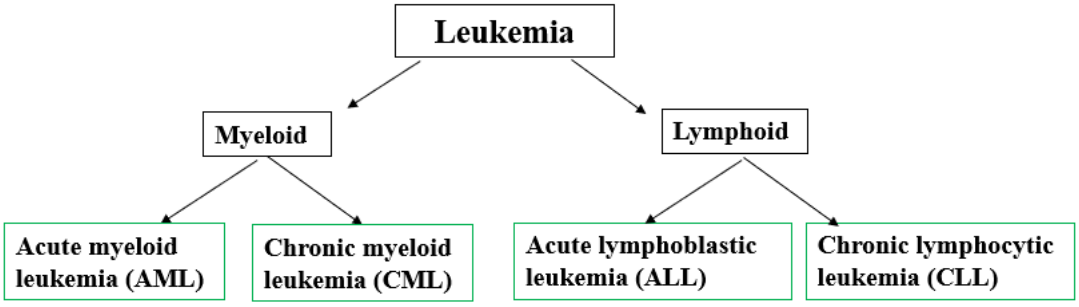
E. Secondary malignancies

- Lymph nodes are the more common site of metastasis, particularly for tumours that tend to spread via lymphatics (vs haematogenous spread)
- Lymph node metastasis is often the single most important prognostic indicator in cancer, and forms part of cancer staging
- Identifying the source of the lymph node metastasis depends on the tumour morphology (including immunophenotype) and likely lymph node drainage sites (e.g. papillary thyroid carcinoma drains to cervical lymph nodes)

III. MYELOID NEOPLASMS

A. Definition and Classification of Leukemias

- **Definition: Leukaemia** = white blood cell neoplasms that are primarily disorders of the **bone marrow** and thus present with widespread involvement of the bone marrow and usually spill into the peripheral blood; can also infiltrate lymph nodes, liver, spleen and other tissues
    - Patients frequent present with signs and symptoms related to **suppression of normal haematopoiesis** in the bone marrow, or bone/joint pain.
    - Can also present with systemic symptoms from release of cytokines (fever, night sweats, weight loss), similar to patients with lymphoma
    - Can sometimes involve lymph nodes and spleen.
- C**lassification**
    - Can be divided into **acute** vs **chronic** leukaemia:
        - **Acute leukaemia**: Symptoms usually related to suppression of normal marrow function; fatal within weeks if untreated. Characterised by immature blast cells
        - **Chronic leukaemia**: Symptoms more non-specific; longer survival if untreated. Associated with more mature well-differentiated cells
    - Can also be divided into **lymphoid** vs **myeloid** leukaemia (see the above section *II. Lymphoid Neoplasms*)



Myeloid neoplasms originate from haematopoietic progenitor cells (precursors of granulocytes, monocytes, erythrocytes or megakaryocytes) and primarily involve the bone marrow. Symptoms therefore usually related to altered haematopoiesis. Three broad categories of myeloid neoplasia are recognized:

1. **Acute myeloid leukaemia (AML)**: immature progenitor cells accumulate in the bone marrow and suppress normal haematopoiesis
2. **Myelodysplastic syndromes (MDSs)**: defective maturation of myeloid progenitors causing ineffective haematopoiesis, leading to peripheral blood cytopenias
3. **Myeloproliferative neoplasms (MPNs)**: increased production of one or more terminally differentiated myeloid elements (e.g., granulocytes), leading to raised peripheral blood counts

Category	Classification	Key features
Acute myeloid leukaemia (AML)	AML with defining genetic aberrations AML with MDS-related features	• Prognosis depends on molecular subtype • Occurs at all ages but incidence increases with age • P/w symptoms related to anaemia, neutropenia and thrombocytopenia (e.g. fatigue, fever, mucocutaneous bleeding)

	AML, therapy-related AML, NOS	• **Diagnosis**: at least 20% myeloid blasts in the bone marrow • **Cytogenetics**: important in classification, especially as particular chromosomal abnormalities correlate with certain clinical features, prognosis and guide therapy
Myelodysplastic syndromes (MDS)	- Primary (idiopathic) vs therapy-related - Based on cytogenetic and morphologic abnormalities	• Prognosis varies; High risk of transformation to AML • Usually older adults (8th decade) • Asymptomatic or p/w symptoms related to pancytopenia
Myeloproliferative neoplasms (MPN)	- Chronic myeloid leukaemia (CML) - Polycythaemia vera (PCV) - Essential thrombocythemia (ET) - Primary myelofibrosis (PMF)	• Can transform to a "spent phase" with marrow fibrosis, cytopenias and increased extramedullary haematopoiesis, or transform to acute leukaemia • Usually adults • P/w varying symptoms e.g. anorexia, fatigue due to increased cell turnover in CML; bleeding and thrombotic episodes due to abnormal blood flow in PCV and ET; marrow failure and splenomegaly in PMF • **Pathogenesis**: Abnormal constitutionally active tyrosine kinases e.g. from the fusion *BCR-ABL* gene in CML (Philadelphia chromosome), mutated *JAK2* in PCV, or other signalling pathway abnormalities, lead to growth factor independent proliferation and survival of marrow progenitors, without impairment of differentiation

IV. HISTIOCYTIC NEOPLASMS

A. Langerhans cell histiocytosis

- Clonal proliferation of a special type of immature dendritic cell called Langerhans cell, commonly associated with *BRAF* mutations
- Can present as a multifocal multisystemic disease (Letterer-Siwe disease), unifocal or multifocal unisystemic disease, or as a pulmonary disease often in adult smokers

V. SPLEEN

A. Basic structure and physiology

- Thin connective capsule enclosing abundant red pulp dotted with white pulp follicles
    - **Red pulp**: Numerous thin-walled vascular sinusoids separated by splenic cords containing many macrophages
    - **White pulp**: Periarteriolar lymphatic sheath (T cells surrounding an artery) with occasional expansion to form B lymphoid follicles that can develop germinal centres in response to antigenic stimulation
- 4 major functions:
    - **Filtration of unwanted elements in blood via phagocytosis**: Spleen is the largest unit of the mononuclear phagocyte system – performs phagocytosis of blood cells that are trapped, and particulate matter within blood e.g. bacteria

- **Antibody production**: Major secondary organ in the immune system and is especially important for production of antibodies against microbial polysaccharides and autoantibodies against self-antigen. Splenic insufficiency e.g. due to splenectomy thus predisposes to sepsis caused by encapsulated bacteria e.g. pneumococci
- **Haematopoiesis**: Minor site during foetal development; can be major site of compensatory extramedullary haematopoiesis in adults
- **Reserve pool /storage space through sequestration of formed blood elements**: Amount of trapped blood elements increased with splenic enlargement

B. Non-neoplastic conditions

- **Splenomegaly** = enlargement of the spleen
  - Most common manifestation of splenic disease
  - Various causes, including infections, splenic congestion due to portal hypertension, involvement by lymphohaematogenous disorders (e.g. lymphomas / leukaemia / anaemia), autoimmune conditions, storage diseases, amyloidosis or other neoplasms
- **Hypersplenism** = increased sequestration and phagocytosis of blood elements by the spleen, usually due to splenomegaly, therefore resulting in cytopenia (anaemia, leukopenia, thrombocytopenia)

Non-specific acute splenitis

- Non-specific transient enlargement of the spleen in any blood-borne infection, due to the microbe as well as the cytokine released in response to the infection

Congestive splenomegaly

- Due to chronic venous outflow obstruction caused by portal or splenic vein hypertension. This can result from hepatic causes (e.g. liver cirrhosis) or extrahepatic causes (e.g. portal vein thrombosis associated with inflammation of the portal vein after intraperitoneal infection, or splenic vein thrombosis due to tumours in adjacent organs)
- **Gross**: Markedly enlarged firm spleen with thickened fibrous capsule
- **Micro**: Congestion of red pulp that becomes increasingly fibrotic and cellular with time

Splenic infarct

- Caused by occlusion of the major splenic artery or its branches, due to absence of collaterals
- Often due to emboli (e.g. from atheroma or infective endocarditis, in which infarcts can be septic instead of bland) or in markedly enlarged spleens (likely due to easily compromised blood supply)
- **Gross**: Subcapsular pale wedge-shaped areas (+/- suppurative necrosis in septic infarcts) with fibrinous exudates on the overlying capsule. With healing, the infarcts convert into depressed scars

Congenital anomalies

- **Asplenia**: Complete absence of spleen; rare. Hypoplasia more common
- **Accessory spleen (splenunculus)**: Common; single or multiple anywhere in the abdomen. Histologically and functionally identical to normal spleen

Splenic rupture

- Usually secondary to blunt trauma; minor trauma can also cause splenic rupture if the spleen is acutely enlarged with a thin capsule and thus fragile from other causes e.g. infectious mononucleosis
- Consequence: Intraperitoneal haemorrhage, requiring emergency splenectomy

C. Neoplasms

- Rare (except for lymphohaematogenous tumours); most common are lymphangiomas and haemangiomas

VI. THYMUS

A. Basic structure and physiology

- Maximum weight during puberty (up to 50g), after which it progressively involutes
- Comprises lobules of
    - outer cortical layer (with spaced out polygonal epithelial cells and more lymphoid cells) and
    - central medulla (closely packed often spindle shaped epithelial cells, sometimes forming Hassall corpuscles with central keratinisation, and fewer lymphoid cells)
- Site of T cell maturation (decreasing role as the organ atrophies with age)

B. Non-neoplastic conditions

Developmental disorders

- **Thymic hypoplasia or aplasia**: seen in DiGeorge syndrome (22q11 deletion syndrome)
- **Isolated thymic cysts**: Uncommon; often incidental and not significant if asymptomatic and other neoplasms have been excluded

Thymic hyperplasia

- 2 types:
    - True thymic hyperplasia: when a morphologically normal thymus is large (increased in weight) for the patient's age, no increase in lymphoid follicles
    - **Thymic follicular hyperplasia**, which refers to the appearance of lymphoid follicles with germinal centres within the thymus, often in association with myasthenia gravis or other autoimmune disorders. Size and weight may be normal

C. Thymoma and thymic carcinoma

- Tumour of thymic epithelial cells, accompanied by varying numbers of benign immature T cells (thymocytes)
- **Clinical features**: Usually in adults >40 years old; present with symptoms of mediastinal compression, myasthenia gravis or incidentally during imaging for other reasons
- **Classification**: Thymomas are classified based on histologic appearance; can be non-invasive or invasive (penetration through the capsule) / metastatic. Thymic carcinoma are most often squamous cell carcinomas

D. Other thymic neoplasms

- Includes germ cell tumours, lymphomas, carcinoids etc.