LYMPHATIC SYSTEM

Prepared by Pharm. Oge Isiogugu

A system is a group/collection of organs that performs a specific function. Lymphatic system is a network of lymph vessels and nodes which transports fluids, fats, proteins and lymphocytes to the blood as lymph and removes microbes/debris from tissues. 2/3 of lymph is derived from the liver. The **CNS/Bone/Superficial layers of the skin** lack a network of lymphatic system. Lymphatic system is part of circulatory system (Cardiovascular/vascular system) and immune system. It is an **open system** [supplies and collects fluid and does not have a central pump unlike vascular (closed) system which has the heart as the central pump]. The circulatory system processes about 20 L of blood daily through capillary filtration which removes plasma and leaves blood cells. About 17 litres of the filtered plasma is reabsorbed back to the blood vessels leaving behind about 3 L of plasma in the interstitial fluid. The lymphatic system serves as an accessory return route for this surplus 3 L of plasma back to the blood stream. The lymphatic system also plays a defensive role in the immune system because of the lymphocytes concentrated in lymph node. The constituents of blood exit the micro vascular blood vessels and become interstitial fluid. When this interstitial fluid enters the lymphatic vessels of the lymphatic system, it is called lymph (**clear liquid**). The lymph vessels empty inside the lymph duct which drains into one of the two subclavian veins.

COMPONENTS OF LYMPHATIC SYSTEM

a. Lymph tissues/organs (also include circulatory lymph)
b. Conducting system (lymphatic vessels)

Lymphatic organ (lymphoid) - We have primary (1º), secondary (2º) and tertiary (3º) lymphatic organs. Lymph tissue is a tissue through which lymph travels.

1º – produces large amount of lymphocytes. They include the **Thymus and Bone marrow**. After birth, Bone marrow is solely responsible for production of RBC. Bone marrow produces B and T cells. B cells enter the 2º lymphoid organs in search of pathogens while T-cells enter the thymus, develop further and join B-cells in search of pathogens. Thymus is the site for maturation of T-cells (the lymphocyte responsible for adaptive immunity). In the absence of thymus, serious immune deficiency and susceptibility to infection occur. One major function of Thymus is induction of central tolerance by allowing selection of functional and tolerant T-cell repertoire. Thymus increases from delivery to puberty and decrease thereafter.

2º - They provide environment for interaction between antigens and lymphocytes. They include **lymph nodes, tonsils, spleen, payer patches and adenoids**. The spleen is the largest lymphatic organ and it is located on left of abdominal cavity. It produces immune cells and fight antigens. It is the site for destruction of red blood cells. It produces blood cells during foetal life and stores RBC and lymph. Spleen is also able to produce lymphocytes. If lymphoid tissues are well organized, it is called lymph node but if it is loosely organised, it is called Mucosal Associated Lymphoid Tissue (**MALT**). Portions of lymph tissue with

increased concentration of lymphocyte is called lymphoid follicle. Lymph nodes (spherical) have both efferent and afferent lymphatic vessels. The outer part of lymph node is **cortex** but the inner part is **medulla**. The efferent lymph vessels arise from the lymph node at **Hilum**. Arteries and veins that supply the lymph node with blood enter and exit through the Hilum. It is a depression on lymph node making it to be Bean-shaped or ovoid. Lymph nodes are found in inguinal region, pelvis, axilla, neck, mediastinum of chest.

3º - They have very little lymphocytes and perform immune functions only when challenged with an antigen which causes inflammation. It imports lymphocytes from blood and lymph to assist it.

Conducting system - They include the **Lymph capillaries** (they are blind end tubes which are more permeable to interstitial fluid contents compared to blood capillaries and they join up to become), **larger lymph vessels** (which are cup-shaped valves to prevent back flow of lymph towards the thorax which then join up to become), **lymphatic ducts** which are dilated and they lie in the root of the neck (the **right** lymphatic duct is about 1 cm and opens into the right subclavian vein and it drains right side of head/neck/arm/thorax while the **left/thoracic** lymphatic duct is about 40 cm and opens into the left subclavian vein and it drains left side of Head, neck, arm, thorax, both legs and pelvic). The lymphatic vessels (channels, lacteals or lymphatics) are responsible for maintaining balance of body fluid.

Development of lymph Tissues

Lymphatic tissues start developing by the end of 5^{th} week of embryonic development. Lymph vessels develop from lymph sack which arises from developing vein, in the following order;

- Paired jugular lymph sack at the junction of internal jugular and subclavian veins
- Unpaired retroperitoneal lymph sack at the mesenteric of intestine and develops from primitive vena cava and mesonephric vein
- Paired posterior lymph sack and develops from iliac veins. All lymph sacks are invaded by mesenchymal cells which turn them to lymph node (except anterior part of the sack where **Cisterna Chyli** develops from)
- The spleen develops from mesenchymal cells between layers of dorsal mesentery of stomach
- The thymus develops as an outgrowth of 3^{rd} pharyngeal pouch

Lymph flow

Lymph flow is determined by:

A. **Activity of lymphatic pump**: active during exercise. Factors that influence these include;

- Intrinsic contraction of lymphatic passages
- Extrinsic compression of lymphatic vessels through external tissue forces
- Skeletal muscle contractions
- Arterial pulsation
- Movement of the body
- Compression of tissue

B. **Interstitial fluid pressure**: decreased interstitial fluid pressure of less than -6mmHg causes low flow but interstitial fluid pressure of up to 0mmHg improves flow. Factors that increase interstitial fluid pressure will increase lymph flow. These factors include;

- Increased capillary pressure
- Increased permeability of capillaries
- Increased interstitial fluid colloid osmotic pressure
- Increased colloid osmotic pressure

Functions of Lymphatic system

1. Removal of interstitial fluid from tissues
2. Absorbs and transports fatty acids and fats as chyle through thoracic/left lymphatic duct
3. Transports WBC into bones
4. Transports antigen-presenting cells (dendritic cells) to the lymph node where immune response is stimulated

Clinical Significance

The lymphatic system is responsible for transporting cancerous cells between different parts of the body through metastasis. The lymph nodes can trap these cancer cells and if they fail to destroy these cells, they become sites of 2^{o} tumours which could lead to:

- Enlarged lymph nodes/lymphadenopathy: This could be local or generalized
- Lymphedema: due to damaged/malfunctioning lymph system leading to accumulation of lymph. Affects mainly the limbs (Elephantitis) though face, neck, pennis/scrotum (presence of filarial worms *Wucheraria bancrofti* and *Bruga malayi*) or abdomen could be affected
- Lymphangomatosis: multiple lesions of the lymph vessels
- Lymphoma: cancer of lymphatic tissues. Could be Hodgkin's which is characterized by Reed-Sternberg cells and occur in younger age groups and Non-Hodgkin's which is the proliferation of B and T cells and occurs in Older age group
- Lymphoid leukaemia: where host is devoid of different lymphatic cell
- Lymphangiosarcoma: malignant tissue tumour
- Lymphangioma: benign tumour
- Lymphangioleiomyomatosis: benign tumour of smooth muscle of the lymphatics of the lungs

Other diseases of lymphatic systems include:

- Lymphyadenitis: inflammation of the lymph nodes as seen in tuberculosis
- Lymphangitis: infection of lymph vessels/channels maybe as a result of complication of bacterial infection

BLOOD

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Blood is a fluid connective tissue that transports oxygen, nutrients and growth factors to individual cells of the body and removes wastes from these organs to the kidney or lungs for elimination. It exits the heart via arteries and enters via the veins. When blood diffuses across capillary walls, oxygen, carbon dioxide and wastes move from the tissues to the blood stream. As oxygen deficient blood leaves the capillary walls/beds, it flows into veins which return it to the heart. The returning blood then flows from the heart to the lungs where it picks oxygen and returns to the heart to be pumped throughout the body once again. Most adults have 4-5 litres of blood for females, for males-5-6 litres.

General properties of Blood

Viscosity of whole blood; 4.5-5.5, plasma; 2.0
Osmolarity; 280-296 mOsm/L
Haemoglobin; 13-18 g/dl for male and 12-16 g/dl for female
Mean RBC Count is Male- 4.6-6.2 million cells/*uL* of blood
Female 4.2-5.4 million cells/*uL* of blood
Platelet count; 130,000-360,000 cells/*uL* of blood
Total WBC Count; 5,000 – 10,000 cells/*uL* of blood
Mean fraction of body wt; 8%
Volume in adult body; male = 5-6 L, female = 4-5 L
Mean temperature; 38^{o}C
PH; 7.35-7.45

Importance of viscosity and osmolarity of blood and protein in blood

Viscosity: resistance of a fluid to flow due to cohesion between its particles. Viscosity partially governs the flow of blood through the vessels. Protein deficiency reduces viscosity and causes blood to flow too easily (increasing blood flow) while excess protein increases viscosity and causes blood to flow too sluggishly (decreases blood flow). Either way, it may cause cardiovascular problems.

Osmolarity: this is a measure of solute concentration and expressed as number of osmoles of a solute per liter of a solution. In other to remove waste substances, the substance must pass between blood stream and tissue fluid through the capillary walls. The rate of re-absorption is governed by relative osmolarity of the blood versus the tissue fluid. If osmolarity is too high blood stream absorbs too much fluid leading to oedema and decrease in blood pressure. It's important that blood maintains optimal osmolarity. The osmolarity of blood is a product of Na^{+}, protein and RBC.

The contribution of protein to blood osmotic pressure is called colloid osmotic pressure and has some significance. Decrease protein of blood plasma leads to decrease

osmolarity, blood loses fluid to tissue, tissue swells and fluid may accumulate in abdominal cavity leading to ascites.

Functions of blood

1. **Transport/distribution**: blood carries oxygen and carbon dioxide between lungs and other organs. It carries nutrients from digestive system and storage depots to other organs. It carries wastes to the liver and kidney for detoxification/removal. It carries hormones from endocrine glands to target cells and carries heat to the skin for removal thereby regulating body temperature.
2. **Protection**: blood plays several roles in inflammation. Leucocytes destroy microbes and cancer cells, antibodies and other proteins neutralize or destroy pathogens. Platelet factors initiate clotting and minimize blood loss.
3. **Regulation**: transfer water to and from the tissue thereby stabilizing water balance and also buffers acids and bases thereby stabilizing the pH of the body. It also regulates body temperature.

Components of blood

They include the **plasma** and **formed elements**. Formed elements are suspended in plasma (non-living fluid matrix). The plasma consists of 55% of the whole blood. It is the least dense component of blood. Formed elements are leucocytes, platelets and erythrocytes. They are called formed elements because they are enclosed by plasma membrane which arises from hematopoietic stem cells and they have definite shape and visible structure. The buffy coat contains the Leucocytes and platelets which make up less than 1% of the whole blood; they protect the body and stops bleeding respectively. Erythrocytes make up 45% of the whole blood, it is the densest component and it transports oxygen. Haematocrit /PCV = % of volume of whole blood that is made up of RBC which is 47%±5% in males and 42%±5% in females. All blood components are cells except platelets which are fragments of certain bone marrow cells. Dark red blood is poor in oxygen; scarlet coloured is oxygen rich. Blood accounts for about 8% of body weight.

Blood plasma contains the following:

- Plasma proteins
- Non-protein nitrogenous substances
- Nutrients
- Electrolytes
- Hormones
- Respiratory gases

Erythrocytes (RBC)

The major function of erythrocytes (RBC) is to transport oxygen and carbon dioxide.

- It contains haemoglobin which is RBC protein that transports respiratory gas (approximately 97%) and also the pigment responsible for the red colour
- It contains spectrin which is a protein that gives it its shape

- Formation process of blood cells known as haematopoiesis /hemopoiesis takes place in red bone marrow (RBM)
- Erythropoiesis is the formation of RBC from myeloid stem cell
- Erythropoietin is the hormone that directly stimulates erythropoiesis
- Raw materials for RBC production are carbohydrates, lipids and amino acid while iron is important for haemoglobin synthesis
- Life span of RBC is 100 -120 days and destroyed in the spleen
- Haemoglobin spilled from RBC destruction is captured by haptoglobin and the complex is phagocytised by macrophages

Leukocytes (WBC)

Types of leucocytes

1. granulocytes (polymorphornuclear leucocytes sometimes)
2. agranulocytes.

Granulocytes include:

a. Basophils (0.5- 1%)
b. Eosinophils (2-4%)
c. Neutrophils (50-70%)

Agranulocytes include:

a. Lymphocytes (25-45%)
b. Monocytes (3-8%)

Key: **N**ever **L**et **M**onkey **E**at **B**ananas (descending order of abundance).

- Only formed elements that are complete cells
- While RBCs are confined in the blood, WBCs slip out of the capillary blood vessels by a process called **diapedis** and with the help of circulatory system, move to areas where they perform inflammatory or immune response
- Life span of granulocytes is 0.25-9 days while agranulocytes vary
- The process of its production is leucopoiesis, stimulated by, Inter-Leukin and colony stimulating factor (CSF)

Neutrophils: These granulocytes take up both acidic/basic dyes. They can phagocytise bacteria too. It is referred to as PMN- leucocytes.

Eosinophils: This kills parasitic worms that are too large to be phagocytised. It plays a complex role in allergy and asthma.

Basophils: this releases histamine and other inflammatory mediators, it contains heparin -an anticoagulant.

Lymphocytes: T-Lymphocytes help in immune response.

B-lymphocytes produce antibodies.

Monocytes: it carries out the process of phagocytosis and develops into macrophages in tissues.

Platelets: they are fragments of megakaryocytes and their formation is stimulated by thrombopoietin (hormone). The life span is less than 10 days unless involved in blood clotting. Its major function is blood clotting.

Disorders of Blood

RBC disorders:

1. Anaemia: blood has low oxygen carrying capacity, this could be caused by:
   a. Insufficient number of RBC as seen in the following
      i. Haemorrhagic anaemia due to blood disorder
      ii. Haemolytic anaemia due to RBC ruptures (in splenomegaly)
      iii. Aplastic anaemia- destruction/inhibition of red bone marrow (RBM)
   b. Decreased haemoglobin content caused by the following (normal level is 14-16 g/dl in males and 13-18 g/dl in females):
      i. Iron-deficiency anaemia, with microcytic and hypochromic RBC
      ii. Pernicious anaemia due to Vit. B12 deficiency with macrocytic RBC
   c. Abnormal haemoglobin which could lead to the following:
      i. Thalassemia where one globin chain is faulty/absent
      ii. Sickle cell anaemia where there is abnormal Hgb, Hbs-s due to change in one of 146 amino acids in β-chain of the globin molecule. **Hydroxymethylbenzoic acid 10 mg (Drepanostat)** is the drug used to treat and prevent SC disease acute crisis. For treatment, it is given 30 mg tds for adults' PO, 20 mg tds for children and 10 mg tds for infants. In preventing crisis, it is given 20 mg tds for adults and children and 10 mg tds for infants (mix with food). Another drug with therapeutic benefit is **Hydroxyurea/Hydroxycarbamide (Droxia).** It comes as 200, 300 or 400 mg capsule and is dosed 15 mg/kg in adults with creatinine clearance > 60 mL/min or 7.5 mg/kg in patients with creatinine clearance < 60 mL/min. It is then increased by 5 mg/kg q12 weeks to a maximum of 35 mg/kg

***Athlete's anaemia** occurs when athlete trains vigorously leading to increased blood volume which dilutes blood components thereby causing false iron deficiency anaemia. This deficiency normalises after a while though.

2. Polycythemia; this is excess (increased) production of RBC thereby increasing blood viscosity. It could be:
   i. Polycythemia vera: a RBM cancer
   ii. Secondary polycythema due to increased erythropoietin production as a result of decreased oxygen availability (which occurs in high altitudes). It can be treated by dilution, i.e. removing blood and diluting with normal saline

   ***Blood doping** is an artificially induced polycythemia, where an athlete withdraws his/her blood. The blood is replaced via erythropoies but when the athletes re-infuses the blood back after few days or weeks, there is increase in PCV leading to increase in oxygen carrying capacity of blood. But this can cause stroke/heart failure.

WBC Disorders are:

1. Leukopenia – decreased WBC
2. Leukaemia- increased WBC. The first 2 are cancerous

3. Infectious mononucleosis (due to EBV)

Note myelocytic leukaemia affects myeloblast while lymphocytic leukemia affects lymphocytes

Platelets Disorders

1. Thrombocytopenia: decreased platelet leading to increased risk of bleeding
2. Haemophilia (A, B, C): A hereditary bleeding disorder due to inability of blood to clot
   A- Factor VIII Deficiency. Known as classic haemophilia.
   B- Factor IX Deficiency. Known as Christmas disease.
   C- Factor XI Absence. Affects both sexes and its mild.
   Factor A and B affects mostly males and its usually severe.

Blood clotting

Homeostasis: blood flows normally in the blood vessel. But if there is a break in the wall of the blood vessels, a cascade of process is activated to stop over bleeding leading to death.

a) Vascular spasm: damaged blood vessels constrict (vasoconstriction of smooth muscle)
b) Platelet plug formation: platelets aggregates and forms plug to temporarily seal the break in blood vessels.
c) Coagulation/blood clotting: fibrin forms a mesh that traps RBC and platelets to form the clot. This 3rd process occurs in 3 phases;

Phase 1: Prothrombin activator (PA) is formed via extrinsic /intrinsic pathway.

Phase 2: PA Converts prothrombin to thrombin.

Phase 3: thrombin catalyses joining of fibrinogen molecules to form fibrin mesh which traps blood cells and seals the hole until the blood vessel is repaired.

Intrinsic pathway	**Extrinsic pathway**
a) Clotting factors are in the blood	Clotting factors are outside the blood.
b) Slower because of many steps	Faster because it bypass several steps.

All factors except III and IV are produced in the liver.

Factor number	**Name**	**Function**
I	Fibrinogen	Converted to fibrin
II	Prothrombin	converted to thrombin, converts fibrinogen to fibrin
III	Tissue factor (Tf)	activates extrinsic pathway
IV	Ca^{2+}	
V	Proaccelerin	
VII	Proconvertin	activates both pathways
VIII	Anti hemophilic factor (AHF)	
IX	Plasma Thromboplastin Component	
X	Stuart factor	
XI	Plasma Thromboplastin Antecedent	
XII	Hageman factor	activation leads to inflammation, activates plasmin, initiates clotting in vitro
XIII	fibrin stabilizing factor (FSF)	Cross links fibrins

After coagulation/clotting, the following occurs;

a) **Clot retraction**; 30-60 min after coagulation, the clot is further stabilized by contraction of platelets which draws the edges of the broken blood vessels together.
b) **Clot repair**: platelet-derived-growth-factor (PDGF) stimulates fibroblast and smooth muscle cells to divide and rebuild the wall.
c) **Fibrinolysis**: this involves the removal of unneeded clot after healing by plasmin.

Genotypes and the consequence

Genotype	Recommendation
AA + AA	Excellent
AA + AS	Good
AA + SS	Fair
AS + AS	Bad
AS + SS	Very bad
SS + SS	Extremely bad (in fact, do not try it)

Blood grouping (ABO and Rh system)

Blood group	Antibody or agglutinin present	Blood that can be received
AB+	None	A+, A-, B+, B-, AB+,AB-, O+, O-
AB-	None	A-,B-, AB-, O-
A+	Anti-B (b)	A+, A-, O+, O-
A-	Anti-B (b)	A-, O-
B+	Anti-A (a)	B+, B-, O+, O-
B-	Anti-A (a)	B-, O-
O+	Anti-A (a) Anti-B (b)	O+, O-
O-	Anti-A (a) Anti-B (b)	O-

*O+ occurs in 1 out of every 3 individuals and has an incidence of 37.4 %, thus it is the most common blood group type. AB- occurs in 1 out of every 167 individuals and has an incidence of 0.6 %, thus it is the rarest blood group type. AB (precisely AB+) is universal recipient (can receive from A, B, AB and O) while O (precisely O-) is universal donor. Agglutination occurs when there is blood incompatibility especially during blood transfusion leading to haemolysis of RBCs and possible death of the patient

Rhesus factor (Rh- factor)

The most important rhesus includes D, E, e, C, and c. Rh (D) is usually used to refer to the Rhesus factor. Most people are Rh D^+ but if a woman is Rh D^- and is pregnant and the baby is Rh D^+, during delivery/after delivery, the placenta detaches and the baby's blood crosses over to the mothers' blood, the mother's blood sees the Rh D^+ blood of the baby as an invading antigen and develops anti-Rhesus antibody to the Rh $D^{+\cdot}$ Now during second pregnancy or subsequent pregnancies, the mother's blood crosses via the placenta to attack the next baby's RBC resulting to **Erythroblastosis Fetalis or Hemolytic disease of the newborn**. This also happens in miscarriages or abortion. To avoid this, Rhogam (Rhesus immunoglobulin) is given to the mother before delivery of the first baby or within 24 hours after the delivery. It contains anti-Rh agglutinins which prevents the mother from developing anti-Rh antibody.

*A foetus RBC Produces Hg-F which has a pair of α and γ chains on each globins molecule which has a higher affinity for oxygen than adults Hg-A which has paired α and β chains.

After birth, the RBC carrying Hg-F is destroyed by liver and the baby's erythroblast start producing Hg-A.

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