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Clinical Insights into the Lymphatic System- Functions and Disorders

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Abstract:- Lymphatics play a crucial role in defense mechanism of the body, but there is a wide array of conditions that directly or indirectly alter lymphatics. Lymphatic disease may manifest as imbalance in body fluid homeostasis, immunity impairment, and irregularities in fluid reabsorption. Lymphadenopathy is a major clinical manifestation associated with infection, inflammation, autoimmune disease and malignancy. It is indicative of systemic infection or disease when there is involvement of specific lymph nodes. Lymphatic vessels, constitute the secondary circulatory system in human body after blood circulation, and plays a significant role in maintaining homeostasis throughout the body. They are responsible for absorption and transport of lymph, the immune defense.

Keywords:- *Lymphatics, Lymphoid, Tissue Fluid, Lymph Nodes, Lymphadenopathy, Blood Vessels, Lymph.*

I. INTRODUCTION

The lymphatic system comprises of vessels and organs which circulates the lymph to and from the tissues and blood vessels. The lymphatics harmonize with the blood vessels, as it distributes the fluids throughout the body and clears the disease- causing agents from the blood.[1] It is a one-way transmit system that is in coordination with the circulatory system. Once formed, the lymph passes through the lymphatic channels from the tissue to the blood; along lymphatic vessels (also called initial lymphatics), precollectors (human skin only), collecting vessels, lymph nodes, trunks and ducts of lymphatic system, and is returned to the blood circulation in lymphatic-vascular junctions in the head and neck area. [2]

II. COMPONENTS OR PARTS OF LYMPHATIC SYSTEM

- *Lymph, The Recovered Fluid*
- *Lymphatic Vessels, Which Transport the Lymph*
- *Lymphatic Tissue, Composed of Aggregates of Lymphocytes and Macrophages that Populate Many Organs of the Body and*
- *Lymphatic Organs.*[1]

- *Lymph*

Lymph is a fluid which is yellowish in colour, clear in nature and is present in the body. The blood plasma passes through the capillaries into the other organs to supply nutrients. After supplying to the peripheral cells, the most of this fluid gets assimilated back into the circulation, while remaining of the fluid is left back in the tissue. This residual fluid is known as the interstitial fluid. The lymphatic capillaries absorb the interstitial fluid, thereby forming the lymph.

Lymph comprises of- water, proteins, lipids, glucose, ions- K,Na,Cl and immune cells. Human body is estimated to produce about 2 litres of lymph in a day, which can vary depending on the physiological and pathological conditions.[1]

- *Lymphatic Vessels*

The lymphatics that carry lymph are called initial lymphatics. They are thin-walled but relatively large in size (10–60 mm) when compared with blood vessels (5–10 mm). They are lined by a single layer of cells known as lymphatic endothelial cells (LECs) and have little basement membrane. These vessels have following layers- tunica interna lined with an endothelium and valve, a tunica media comprising of elastic fibres and smooth muscle and thin outer tunica externa. [4]

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Lymphangion is a component of the vessel that is present in between two valves. These are supplied by both sympathetic and parasympathetic nerves, and are responsible for rhythmic pulsations. In human body, they are present in the cervical region. The average diameter of lymphangion is 0.2 mm and is 2 mm long .[6]

In the cervical region, these vessels can be classified into two types; superficial and deep. The lymph from this region is drained by superficial vessels. The cervical lymph nodes give rise to the deep lymphatic vessels of head and neck region and they lead to formation of lymphatic trunks- right and left. On the left side, the jugular lymphatic trunk unites with the thoracic duct and drains into the venous system through the subclavian vein. On the right side, the jugular lymphatic trunk forms the right lymphatic duct at the root of the neck and empties into the venous system through the subclavian vein.[4]

➢ *Lymphoid Organs and Immunity*

It is classified into groups; primary, secondary and tertiary lymphoid organs depending on their function and structural cells.

Primary lymphoid organs- These are important for the development and differentiation of the lymphocytes. The bone marrow and the thymus are the two major primary organs. The bone marrow gives rise stem cells that are responsible for formation of lymphocytes. Lymphocytes are of two types- B and T cells. B cells entirely mature and differentiate in the marrow. Whereas, the T cells arising from the marrow stem cells migrate to the thymus for their differentiation. This phenomenon that leads to the development of lymphocytes- both B and T cells is known as antigen-native development. Once the cells are formed, they migrate to all parts of the body through the bloodstream, reaching the secondary lymphoid organs.

Spleen, tonsils, vermiform appendix, lymph nodes, specialized lymphoid tissue of the mucosae (MALT), peyers patches, adenoids constitute the secondary lymphoid organs. Cells migrate from primary organs to secondary lymphoid organs in order to meet the antigens to where they mature. This process is called as the antigen-dependent activation. This process enables lymphatics to fight against specific antigens.

There is another set of lymphoid organs known as tertiary lymphoid organs (TLOs) that resemble lymph nodes. These are present in tissues at the periphery mostly in cases of- chronic infection, transplanted organs undergoing graft rejection, cancers, and autoimmune conditions. These organs typically contain lesser lymphocytes, and play a role in immunity when exposed to antigens thereby leading to inflammation. [2,3,4]

III. LYMPH NODES

These belong to secondary lymphoid organs present in the whole body, and are categorized depending on their location in body (e.g. axillary, pelvic, mediastinal lymph nodes). An individual is estimated to have an average of 450 lymph nodes.

The lymph nodes consist of lymphocytes and other cells (e.g. macrophages, plasmocytes, dendrocytes). Because of the presence many immune cells present, the lymph nodes act as purifier for the lymph. When these cells sense and recognize a pathogen in the lymph (e.g. microorganism), it starts the immune response in order to stop the pathogen from circulating throughout the body. [1,2]

➢ *Anatomy-*

Lymph nodes are structures that resemble bean shape and are about 0.1 – 2.5 cm in length. It is surrounded by a capsule and has concavity on one side along long axes known as the hilum. The nutrients and lymphocytes are carried by arteries and they enter the lymph node through the hilum and veins leave from it.

The lymph node has three zones - CORTEX, PARACORTEX and the MEDULLA.

Cortex is the region where lymphocytes aggregate. According to population of cells present, they can either be primary or secondary. Primary follicles contain lymphocytes that are smaller and inactive whereas secondary lymphoid follicles comprise of active lymphocytes which proliferate and are responsible for the formation of germinal centre. The germinal centre has affinity for cell maturation.

Paracortex is present below the cortex and above the medullary layer. It contains CD4 (cluster of differentiation) and CD8 subsets of T cells.

Medulla is the innermost region. The lymphocytes present form irregular medullary cords and contain plasma cells, lymphocytes and macrophages.[1,2,3]

➢ *Cells*

The lymphocytes constitute a large portion of body's immunity. They are derived from the precursor cells of the primary lymphoid organs. The mature lymphocytes migrate mainly to the secondary lymphoid organs. Their function is to develop a specific immune reaction against the antigens. B lymphocytes attack the antigens by an indirect action, by generating antigen-specific antibodies. On the other hand, T lymphocytes and Natural Killer cells directly kill antigens.

The cells lining the venules are specially adapted in a way that lets the lymphocytes to freely circulate from the blood and these are known as high endothelial venules (HEVs). [7]

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➢ *Mechanism of Lymphatic Flow-*

Blood circulating through the body escapes through capillaries draining into the tissues. This portion of plasma that escapes is known as interstitial fluid. Lymphatic capillaries soak the excessive tissue fluid and transport it via lymphatic pathway. When this extracellular fluid enters the lymphatic system, it is called as a lymph.

The flow of lymph is governed by forces that influence the venous flow. Other factors that influence the flow of lymph are- rhythmic contractions of lymphatics, skeletal muscle pump, presence of arterial pulsations, action of thoracic pump.

Flow inside the initial lymphatics is assumed to be enhanced by changes in interstitial fluid pressure and by the negative pressure of the collecting lymphatics flowing downstream. [8]

➢ *Functions of Lymphatics-*

- It helps in transport of tissue fluid from tissues to other body parts.
- It facilitates movement of fatty acids and fats as chyle from the gastric system
- It facilitates migration of leukocytes to and from the lymph nodes.
- The lymph allows the movement of antigen-presenting cells, such as dendritic cells, to the lymph nodes where an immune response is detected.
- To movement of tissue fluids from all the tissues of the body, circulate it back to the veins in the blood system.
- Plays a crucial role in returning plasma proteins to the bloodstream.
- Lymph nodes are of significant to the defence mechanism of the body. They filter out microorganisms and foreign substances such as toxins. [3,4]

IV. CLINICAL ASPECTS

For the diagnosis and management of cancers, it is crucial to study lymphatic drainage of different organs. As the lymphatic system is in association with other tissues and fluids, it facilitates the transport of different cells throughout the body.

➢ *Lymphadenopathy (Enlarged lymph nodes)*

It implies to one or more enlarged lymph nodes in the body. It can either be localised or generalised depending on the nodes affected. Causes of Generalised lymphadenopathy are- infectious mononucleosis, tuberculosis and HIV, connective tissue diseases such as Systemic Lupus Erythematosus and rheumatoid arthritis, and cancers of tissue within lymph nodes and metastasis of cancerous cells from other parts of the body.[17,18,19]

It is manifested by the enlargement of one Lymph Node compartment and one or more cell types that increase in number and become predominant. It is most frequently associated with following diseases- sarcoidosis, lupus erythematous, rheumatoid arthritis, Castleman disease, angioimmunoblastic hyperplasia, drug hypersensitivity, Rosai-Dorfman disease (RDD), silicone lymphadenopathies, and dermatopathic lymphadenopathies. [9]

Other causes of lymphadenopathy are leukemia, Kawasaki disease, lymphoma and malignancies, collagen disorders, autoimmune lymphoproliferative disorder, Hemophagocytic Lymphohistiocytosis.[15]

Lymph node enlargement is a common finding on physical examinations of children. The absence of palpable lymph node in association with other symptoms suggestive of infection should be considered as presence of immunodeficiency disease. Lymphadenopathy is rather a symptom and not a disease.

➢ *Lymphadenitis*

It is a condition, manifesting non-specific or specific features suggestive of causative agent (bacteria, virus, protozoa). Clinical features- presence of tender and sometimes painful swelling which can be acute or chronic in nature. Localized lymphadenitis is mostly infectious in nature.[17]

➢ *Acute Lymphadenitis*

It is manifested by fast growing, painful and tender swelling of the involved Lymph Nodes. The most common cause- bacterial infections. It produces regional suppurative lymphadenitis. Kikuchi-Fujimoto disease (KFD) is a self-constraining, acute, lymphadenitis mostly noted in young women. It generally affects Lymph Nodes of head and neck region and clinically resembles bacterial lymphadenitis.

➢ *Chronic Lymphadenitis*

It is a constant Lymph Node enlargement which is gradual in onset (3–6 months or more).

The most common cause- Idiopathic. It clinically resembles a neoplastic process. Other causes can be due to presence of cytomegalovirus, chlamydia, Treponema, fungi, HIV, and autoimmune diseases; in others the aetiology remains unknown.[9]

➢ *Lymphedema*

Any damage to lymphatic system can lead to accumulation of lymph which clinically manifests as a swelling, known as lymphedema. It commonly affects the limbs, face, neck and abdomen. In an extreme state, it is called elephantiasis, where the swelling increases in a way that the skin thickens resembling the skin of elephant.

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The clinical features vary from reduced immune responses and impaired metabolic status to the presence of the taxing or weaking form of regional swelling - lymphedema.[10]

Nonne–Milroy's lymphedema is manifested by unilateral or bilateral swelling in different parts of body- legs, arms, and/or face with gradual and irreversible fibrotic changes. In 1898, Meige reported cases of lymphedema in which the age of onset was reported to be after puberty, and it was associated with acute cellulitis. It is also referred to as Meige's syndrome.[11]

Lymphedema is a noted as a clinical manifestation of following diseases- Gorham's disease, Hennekam's syndrome, Intestinal lymphangiectasia, Klinefelter's syndrome, Klippel–Trenaunay syndrome, Lymphedema–distichiasis, hypoparathyroidism, Neurofibromatosis, Protein-losing enteropathy, Stewart–Treves syndrome, Triploidy syndrome, Turner's syndrome. Precise identification and distinction from the non-lymphatic forms of edema depends on the clinical signs such as peau d'orange and the presence of a positive Stemmer sign (inelasticity of the skin at the base of the digits).[12] It is reported that lymphedema can occur after lymph nodes have been surgically removed in the armpit (it leads to swelling of arm due to poor lymphatic drainage) or groin region (leads to swelling of the leg). Conventional management includes manual drainage and use of compression garments. Two drugs that have proven to be successful in treating this condition in clinical trials are: Lymfactin and Ubenimex/Bestatin.[2]

It is still considered as a chronic debilitating disease that is commonly misdiagnosed, either treated too late or not treated at all.

➢ *Inflamed Palatine Tonsils (Tonsillitis)*

Viral or bacterial infections can lead to inflammation of the tonsils. Tonsils appear red in hue and enlarged.

Treatment for Chronic infection of the tonsils includes their removal also known as tonsillectomy. While performing the procedure, care must be taken in order to prevent injury the external palatine vein and the tonsillar branch of the facial artery as it is close to the lymph nodes.

In cases where infection spreads to the peritonsillar tissue, it can lead to formation of abscess. This in turn causes deviation of the uvula, known as quinsy. Quinsy should be treated as a medical emergency, as it can lead to the obstruction of the pharynx thereby causing breathing difficulties. It is treated by draining the abscess and use of the antibiotics. [1]

- The deep cervical lymph nodes lie on the internal jugular vein. They become adherent to the vein in cases of neoplasia or tuberculosis. Therefore, at times of the operation on such patients the vein is also resected. [1]
- The submandibular lymph nodes can become swollen and tender due to the infections in tongue or by tubercular bacteria. [1]
- Spinal accessory nerve may get entangled in enlarged lymph nodes present in the posterior triangle of neck. One must be cautious while taking the biopsy so as to not injure the accessory nerve or the trapezius. [1]
- Cancer from stomach may metastasize to virchow's lymph node (left supraclavicular nodes) and it may become palpable. [1]

➢ *Lymphoma*

It refers to neoplasia arising from lymphatic tissue. Lymphoid leukemias and lymphomas belong to a group of tumours originating from cells of same lineage. It is referred as "leukaemia" when it occurs in the blood or marrow and "lymphoma" when in lymphatic tissue. Both of the above conditions are designated under the "lymphoid malignancy".

Lymphoma can either be Hodgkin lymphoma or non-Hodgkin lymphoma. Hodgkin lymphoma is manifested by a presence of specific cell known as Reed–Sternberg cell, which is visible under microscope. It is commonly associated with Epstein–Barr virus, and manifests as a painless "rubbery" enlargement. It is staged using Ann Arbor staging. Treatment includes -Chemotherapy (ABVD regimen) and radiotherapy. Non-Hodgkin lymphoma is a type of cancer manifested by enhanced proliferation of lymphocytes, occurring in an older group of individuals. Hodgkin lymphoma has better prognosis than Non-Hodgkins lymphoma.[20]

ABVD is a combination chemotherapy therapy to treat Hodgkin's lymphoma made up of four drugs.

- doxorubicin hydrochloride (Adriamycin) - 25 mg
- bleomycin sulfate - 10 units
- vinblastine sulfate - 6 mg
- dacarbazine- 375 mg

➢ *Lymphangioma*

It is a malformation of the lymphatics affecting since birth. It is usually noted in the first 2 years of individual's life. [13] Lymphangiomatosis is the formation of multiple malformations.

They are classified depending on the size and depth of formation at the site. The smaller, superficial form are known as lymphangioma circumscriptum, while the deeper lesions are classified as cavernous lymphangiomas and cystic hygromas.

Cavernous lymphangiomas is characterized by presence of large, loosely defined masses of soft tissue with dilation in the dermis, subcutaneous tissue, and intermuscular septa. Cystic hygromas are fluid-filled lesions that are formed when jugular lymphatic ducts fail to meet and drain into the veins, thereby stagnating the tissues with lymphatic fluid. There is enlargement of sacs that is filled by lymphatic vessels therefore leading to formation of definitive lesion. They are similar to cavernous lymphangiomas, but the hygromas are mostly enveloped by a fibrous capsule.[13] The common sites are the lymphatico–venous junctions, which force fluid to get

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stored in dilated lymphatics, thereby leading to formation of lymphedema.[14]Cystic hygromas are commonly associated with other conditions, including Turner's syndrome, Klinefelter's syndrome, and various trisomies.[13] Treatment of choice- Surgical excision.

➢ *Lymphangiosarcoma*

It is a tumour involving the soft tissues that is malignant as compared to lymphangioma which is a benign tumour occurring frequently in association with Turner syndrome. Lymphangioleiomyomatosis (LAM) is a tumour of the smooth muscles of the lymphatics which commonly manifests in the lungs. It is benign in nature.Clinical features- formation of pulmonary cysts and angiomyolipomas, tumors comprised of specific cells responsible for this condition, adipose tissue, and underdifferentiated blood vessels.[16] LAM is an extremely rare disease, found in fewer than 1 in a million individuals. It affects mainly middle-aged women.

➢ *Castleman disease (CD)*

These belong to collection of rare lymphoproliferative disorders that manifest as presence of lymphadenopathy, along with inflammatory symptoms.

To consider castleman disease as autoimmune condition is not known. Benjamin Castleman, was the first one to describe the disease in 1956.

It has three distinct subtypes:

- unicentric Castleman disease (UCD)
- human herpesvirus 8 associated multicentric Castleman disease (HHV-8-associated MCD)
- idiopathic multicentric Castleman disease (iMCD).

All of the different types involve formation of cytokines and proteins along with unusual lymph node changes that can be noted under the microscope.[21]

➢ *Chylothorax*

It is an unusual accumulation of chyle. Chyle is a kind of lymph rich in lipid that accumulates in the space around the lung. Normally the lymphatics of the digestive system absorbs the lipid from the intestine through the thoracic duct, to drain into the left brachiocephalic vein. When disruption of thoracic duct occurs due to any obstruction or rupture, chyle might leak and accumulate in the pleural spaces. In people consuming balanced diet, this fluid accumulation can sometimes be noted by its turbid, milk like white in appearance, as chyle is comprised of emulsified triglycerides. [22,23,24]

➢ *Kawasaki Disease (Also Known as Mucocutaneous Lymph Node Syndrome)*

It is a condition of unknown cause characterized by fever and occurs in children of around 5 years. There is inflammation of medium-sized blood vessels noted throughout the body. The fever in this syndrome is present for around five days and does not improve by intake of medications. Other symptoms – lymphadenopathy in the head and neck, a rash in the genital area, lips, palms, or soles of the feet, and reddening of eyes. Peeling of the skin from the hands and feet is common after which recovery occurs. This condition is the one of the major etiology of acquired heart disease in children in developed countries. [25, 26]

➢ *Kikuchi Disease*

Other names- histiocytic necrotizing lymphadenitis, Kikuchi necrotizing lymphadenitis, phagocytic necrotizing lymphadenitis, subacute necrotizing lymphadenitis, and necrotizing lymphadenitis. It is observed to occur sporadically in individuals and is not inherited condition.

Dr Masahiro Kikuchi (1935–2012) was the first one to describe the condition in 1972 in Japan followed by Y. Fujimoto. Clinical features of Kikuchi disease - fever, lymphadenopathy, rashes, and headache. In majority of cases, lymphadenopathy occurs in the lymph nodes in neck region with size ranging between 1-2 cms, but sometimes size up to 7 cms has been observed. In few of the cases, the supraclavicular and axillary lymph nodes were found to be swollen as well. [27,28,29,30]

➢ *Lymphangitis*

It is a condition characterized by an infection of the lymphatic channels at a site distal to the channel. It should be treated as medical emergency as the infection can spread rapidly.

The most common cause of lymphangitis is bacteria and can lead to sepsis and death if left untreated. Among the bacteria, Streptococcus pyogenes (Group A strep) and hemolytic streptococci are the causative agents. It can also be caused by viruses- mononucleosis or cytomegalovirus, as well as specific conditions such as tuberculosis or syphilis, and the fungus Sporothrix schenckii. The wound may be small or it may manifest as an abscess. Patients presents with following symptoms- fever, chills, muscular pain, lymphadenopathy and headache. The distinguishing feature of this condition is erythematous, irregular cutaneous streaks in the affected part of the body. Infection may spread within hours and can lead to sepsis and death of the patient.[18,33]

➢ *Lymphatic Filariasis*

It is a condition caused by filarial worms. Majority of cases are asymotomatic, but few individuals may manifest with enlargement of arms, legs, breasts, or genitals which is also known as elephantiasis as it resembles elephant skin. The condition may become painful. Around the world, 129 million patients are afflicted by filariasis accounting for its global condition. This debilitating condition is characterized by impaired lymphatic function and lymphangiectasia. [31]

It is a type of mosquito-borne diseases in which the worms spread after the infected mosquito bites an individual. There are three different types of worms that are the causative agents: Wuchereria bancrofti, Brugia malayi, and Brugia timori, the most common one being Wuchereria bancrofti. These parasites destroy the lymphatics by lodging within the vessels and degrading the immune system of individual. They persist within the body for a period as long as 8 years, while reproducing large numbers of larvae that disseminate in the body through the blood. [32]

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➢ *Intestinal Lymphangiectasia*

It is an uncommon condition that manifests with presence of severe swelling, thickening of small-bowel wall, ascites, and pleural effusion.[34] Patients may present with generalized swelling because of hypoproteinemia as the proteins can be lost to the GI tract.[33] The syndrome can be primary due to presence of a congenital lymphatic vascular disorder, or secondary, as a result of inflammatory or cancerous involvement of the lymphatics. Yang and Jung propose that intestinal lymphangiectasia may develop when lymphatic obstruction involves a segment of the bowel.[35,36]

➢ *Lymph Node Metastasis*

The condition is serious as it decreases the survival span of patients. For those having this recurrent condition and who have had recent surgery, the survival rate is less than 5%. [1]

➢ *Lymphangiomatosis*

It is a disease in which there are multiple cysts or lesions arising from lymphatic vessels. The lymphatic channels which are unusually dilated lymphatic channels lead to formation of cysts. Majority of cases affect multiple organs. It manifests by the age of 20years and is benign in nature, these irregular lymphatics invade surrounding tissues due to involvement along with the compression of adjacent structures. This disorder affects multi-systems of the body. Individuals are generally asymptomatic, but gradually lymphatic channels proliferate leading to enlargement and penetration into surrounding tissues, bone, and organs. Clinical features - wheezing, cough, and dyspnoea, which is often misdiagnosed as asthma. Pathological fracture may result because of the bone involvement. Symptoms may go unnoticed, until the disease process has progressed to a stage where it leads to compression of vital vessels and nerves. [37,38,39,40]

V. CONCLUSION

The lymphatic system is a specialized system with defense function.

The lymphatic system plays a significant role in maintenance of body fluid balance by circulating the body fluid and proteins throughout the body.

The lymph allows the movement of the heavier peptides that are unable to pass via the capillary wall and helps it to enter the blood.

It also has a significance in immunity of the body and removing pathogens out of the body.

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