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A Review On Lymphoma

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Abstract: Lymphoma is a complex group of hematologic malignancies originating from lymphocytes, encompassing Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Each subtype presents distinct biological, clinical, and pathological characteristics, necessitating precise diagnostic and therapeutic approaches. Advances in molecular biology and immunology have significantly enhanced our understanding of the mechanisms underlying lymphomagenesis, including genetic mutations, epigenetic alterations, and immune dysregulation. These discoveries have led to refined classification systems and improved risk stratification.

Diagnostic approaches for lymphoma have progressed with the integration of advanced imaging, immunophenotyping, and molecular profiling techniques, enabling more accurate subtype identification and prognostication. Standard therapies, such as chemotherapy and radiotherapy, remain foundational, but the treatment landscape has shifted with the advent of targeted therapies and immunotherapeutics. Monoclonal antibodies, immune checkpoint inhibitors, and bispecific T-cell engagers have improved response rates and survival outcomes. Furthermore, chimeric antigen receptor (CAR)-T cell therapy has shown remarkable efficacy in relapsed or refractory cases, offering durable remissions in patients with limited options.

This review synthesizes recent progress in lymphoma research and clinical care, emphasizing the critical role of precision medicine and emerging therapeutics in addressing unmet needs.

Index Terms - Lymphoma, Hodgkin Lymphoma, Non-Hodgkin Lymphoma

I. INTRODUCTION

Lymphoma refers to a group of blood cancers that originate in the lymphatic system, an integral part of the immune system. This network, comprising lymph nodes, the spleen, thymus, and bone marrow, plays a key role in defending the body against infections and diseases. In lymphoma, lymphocytes—specialized white blood cells—grow abnormally and accumulate in lymphatic tissues, impairing normal immune function and potentially spreading to other parts of the body[1].

The disease is broadly classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Hodgkin lymphoma is defined by the presence of Reed-Sternberg cells, a specific type of abnormal cell visible under a microscope. Non-Hodgkin lymphoma, on the other hand, encompasses a wide spectrum of lymphatic malignancies with varying biological behaviors and clinical presentations, ranging from slow-growing to aggressive forms[2].

Lymphoma is one of the most prevalent cancers worldwide, with its occurrence influenced by factors such as age, genetic predisposition, immune status, and environmental exposures. Advances in medical research have significantly improved our understanding of lymphoma's biology, leading to more precise diagnostic techniques and innovative treatment approaches[3].

II. TYPES OF LYMPHOMA:

2.1 Hodgkin Lymphoma (HL)

Hodgkin lymphoma (HL) is a type of cancer that originates in the lymphatic system, a crucial part of the immune system. It is defined by the presence of abnormal, malignant cells known as Reed-Sternberg cells, which are large B lymphocytes. Although rare, Hodgkin lymphoma is highly treatable, particularly when detected early. It accounts for approximately 10% of all lymphomas and shows a bimodal age distribution, with peaks in young adults (ages 15–35) and in individuals over 55 years. The disease is slightly more common in males than females[4].

The exact cause of Hodgkin lymphoma is not fully understood, but several risk factors have been identified. Infection with the Epstein-Barr virus (EBV) is strongly associated with the disease, and individuals with a family history of lymphoma are at a higher risk. A weakened immune system, such as in those with HIV/AIDS or those taking immunosuppressive medications, can also increase susceptibility. Lifestyle factors, including smoking and exposure to certain chemicals, may contribute in some cases.

Hodgkin lymphoma is classified into two main categories: classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).

Despite its seriousness, Hodgkin lymphoma is one of the most treatable cancers, with high survival rates due to advancements[5]

2.1.1 Classical Hodgkin Lymphoma (CHL)

Classical Hodgkin lymphoma (CHL) is the most prevalent subtype of Hodgkin lymphoma, accounting for about 95% of cases. It is defined by the presence of Reed-Sternberg cells, which are large, abnormal B lymphocytes typically surrounded by a mixed inflammatory cell background, including T cells, eosinophils, and macrophages. These cells contribute to the tumor microenvironment and the characteristic features of CHL. The exact cause of CHL remains unclear, but it has been strongly associated with Epstein-Barr virus (EBV) infection in many cases. CHL is most common in young adults and has a slight male predominance. It often presents as painless lymphadenopathy, commonly involving the cervical or supraclavicular lymph nodes. Other symptoms may include fever, night sweats, unexplained weight loss (referred to as "B symptoms"), and generalized pruritus[6].

2.1.1.1 Subtypes Of Classical Hodgkin Lymphoma

Descriptive Statics has been used to find the maximum, minimum, standard deviation, mean and normally distribution of the data of all the variables of the study. Normal distribution of data shows the sensitivity of the variables towards the periodic changes and speculation. When the data is not normally distributed it means that the data is sensitive towards periodic changes and speculations which create the chances of arbitrage and the investors have the chance to earn above the normal profit. But the assumption of the APT is that there should not be arbitrage in the market and the investors can earn only normal profit. Jarque bera test is used to test the normality of data.

TYPES	CHARACTERICSTICS
Nodular Sclerosis HL	• Affects 70 percent of patients with cHL • Often causes involved lymph nodes to form nodules (lumps) separated by broad bands of fibrotic (fiber-like) or sclerotic (hardened) tissue • Typically affects young adults and is more common in women • Most frequently involves lymph nodes in the chest.
Mixed Cellularity HL	• Affects 20 to 25 percent of patients with CHL • Characterized by many classic RS cells mixed with various other types of inflammatory cells • Primarily affects older adults, children under 10 years, and people with underlying immunodeficiency disorders

Lymphocyte Rich HL	• Affects five percent of patients with cHL. • Characterized by many normal lymphocytes and relatively few RS cells. • More common in mens
Lymphocyte Depleted HL	• Affects less than one percent of patients with cHL • Characterized by very few normal lymphocytes and many RS cells • More common in older adults • Often not diagnosed until the disease is in an advanced stage

2.1.2 Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare subtype of Hodgkin lymphoma, accounting for approximately 5% of all cases. Unlike classical Hodgkin lymphoma, it is characterized by the presence of popcorn-shaped cells known as lymphocyte-predominant or "LP" cells (formerly called L&H cells), rather than Reed-Sternberg cells. NLPHL typically presents as painless swelling of lymph nodes, often in the cervical, axillary, or inguinal regions, and tends to progress slowly. It is more common in males and often affects individuals in their 30s to 50s. Unlike classical Hodgkin lymphoma, NLPHL is rarely associated with Epstein-Barr virus (EBV). Most patients with NLPHL do not experience systemic "B symptoms" such as fever, night sweats, or weight loss, which are more typical of other types of Hodgkin lymphoma[7].

2.2 Non Hodgkin Lymphoma (NHL)

Non-Hodgkin lymphoma (NHL) is a diverse group of blood cancers that originate in the lymphatic system, involving abnormal growth of lymphocytes, a type of white blood cell. Unlike Hodgkin lymphoma, NHL does not feature Reed-Sternberg cells. It is significantly more common than Hodgkin lymphoma and comprises multiple subtypes, broadly categorized based on the type of lymphocyte involved: B cells or T cells. B-cell lymphomas, such as diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, are the most prevalent, while T-cell and natural killer (NK) cell lymphomas are less common. NHL can develop in lymph nodes, as well as extranodal sites like the stomach, intestines, skin, or brain. Symptoms may include painless lymph node swelling, fever, night sweats, weight loss, fatigue, and, in some cases, specific organ-related symptoms depending on the site of involvement.

The causes of NHL are not entirely understood, but certain factors increase risk, including immunosuppression (e.g., HIV/AIDS, organ transplantation), autoimmune diseases, infections such as Epstein-Barr virus or Helicobacter pylori, and exposure to chemicals[8].

2.2.1 Types of Non Hodgkin Lymphoma

2.2.1.1 Diffuse Large B-Cell Lymphoma (DLBCL)

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of NHL, accounting for about 30-40% of all cases. It is an aggressive lymphoma that originates from B-cells, the immune cells responsible for producing antibodies. DLBCL can present in lymph nodes, but it may also involve extranodal sites such as the gastrointestinal tract, skin, and bone marrow. Symptoms often include swollen lymph nodes, fever, weight loss, and night sweats[9].

2.2.1.2 Follicular Lymphoma

Follicular lymphoma is a common type of indolent B-cell lymphoma, characterized by a slow growth rate. It originates from germinal center B-cells, which are found in the follicles of lymphoid tissues. This lymphoma typically presents in lymph nodes, though extranodal involvement can also occur. Patients may be asymptomatic for long periods, but when symptoms do appear, they can include painless lymphadenopathy, fatigue, and occasional fever. Despite its indolent nature, follicular lymphoma can transform into a more aggressive form, often resembling DLBCL[10].

2.2.1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) are closely related entities, both originating from mature B-cells. CLL typically manifests in the blood and bone marrow, while SLL primarily affects lymph nodes. These two forms are considered different presentations of the same disease.

CLL/SLL is an indolent lymphoma that primarily affects older adults and is characterized by the accumulation of small, mature lymphocytes. Patients often present with asymptomatic lymphadenopathy or splenomegaly, although some may experience fatigue, frequent infections, or weight loss[11].

2.2.1.4 Mantle Cell Lymphoma (MCL)

Mantle Cell Lymphoma (MCL) is a rare and aggressive B-cell lymphoma that arises from the mantle zone of the lymphoid follicles. MCL often presents with widespread involvement, including the lymph nodes, spleen, bone marrow, and gastrointestinal tract. Unlike other B-cell lymphomas, MCL tends to be more difficult to treat and has a poorer prognosis. The disease is characterized by the translocation of genes (often t(11;14)), leading to overexpression of cyclin D1, a protein involved in cell cycle regulation[12].

2.2.1.5 Burkitt Lymphoma

Burkitt lymphoma is a very aggressive form of B-cell lymphoma characterized by rapid tumor growth. It is often associated with the Epstein-Barr virus (EBV) and is commonly seen in children and young adults, particularly in Africa, where it is associated with malaria. Burkitt lymphoma typically presents with a mass in the abdomen, jaw, or pelvis and is highly sensitive to chemotherapy[13].

2.2.1.6 Primary Mediastinal B-Cell Lymphoma (PMBCL)

Primary Mediastinal B-Cell Lymphoma (PMBCL) is a subtype of DLBCL that primarily affects the mediastinum (the area between the lungs), often in young women. PMBCL is an aggressive form of lymphoma that can cause symptoms related to mass effects, such as shortness of breath, chest pain, or superior vena cava syndrome. The lymphoma is distinct from other DLBCLs due to its unique clinical features, including its association with certain genetic mutations[14].

2.2.1.7 Anaplastic Large Cell Lymphoma (ALCL)

Anaplastic Large Cell Lymphoma (ALCL) is a type of T-cell lymphoma, which is relatively rare and aggressive. It can present as either systemic or cutaneous lymphoma. ALCL can be characterized by the presence of large, anaplastic (abnormally shaped) cells, and it may involve lymph nodes, skin, lungs, and other organs[14].

2.2.1.8 Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS)

Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS), is a heterogeneous and aggressive group of T-cell lymphomas that do not fit into any specific category. PTCL-NOS can affect any part of the body and is often diagnosed after excluding other T-cell lymphomas. Symptoms can include swollen lymph nodes, fever, weight loss, and skin rashes[15].

2.2.1.9 Extranodal NK/T-Cell Lymphoma

Extranodal NK/T-cell lymphoma is a rare and aggressive lymphoma associated with natural killer (NK) cells or cytotoxic T-cells. It commonly affects the upper respiratory tract, such as the nasal cavity, and may also involve the skin and gastrointestinal tract. This lymphoma is most frequently seen in Asia and Latin America, and it is often associated with Epstein-Barr virus (EBV) infection[15].

III. EPIDEMIOLOGY AND RISK FACTORS

The incidence of NHL is higher in men than in women, with a male-to-female ratio of about 1.5:1. This gender disparity is more pronounced in certain subtypes like mantle cell lymphoma and diffuse large B-cell lymphoma (DLBCL). Age is another critical factor, as the risk of NHL increases with age, with the median age at diagnosis around 67 years in the United States. While NHL can occur at any age, certain subtypes, such as Burkitt lymphoma, are more commonly diagnosed in children or young adults, especially in regions where the disease is endemic, such as parts of Africa.

Several risk factors contribute to the development of NHL, including immunosuppression, infections, radiation exposure, and chemical exposure. People with weakened immune systems, such as those with HIV/AIDS or those who have undergone organ transplants, are at significantly higher risk for developing NHL. Chronic infections, especially with the Epstein-Barr virus (EBV) and Helicobacter pylori, are strongly associated with certain subtypes of NHL, including Burkitt lymphoma and gastric lymphoma. Other risk factors include long-term exposure to chemicals like pesticides and solvents, as well as previous radiation exposure, particularly in childhood cancer survivors. Genetic factors also play a role, with a family history of NHL or inherited immunodeficiencies increasing susceptibility[16].

IV. DIAGNOSING AND STAGING OF LYMPHOMA

The diagnosis of lymphoma involves a combination of clinical evaluation, imaging studies, and laboratory tests. Initially, a detailed medical history and physical examination help identify symptoms such as swollen lymph nodes, fever, and weight loss. A biopsy of the affected lymph node or tissue is essential for confirming the diagnosis and determining the subtype, aided by histopathological examination. Imaging studies like CT, MRI, and PET scans are used to assess the extent of the disease and stage it. A bone marrow biopsy may be

performed to check for marrow involvement. Additionally, flow cytometry and immunohistochemistry help classify the lymphoma by analyzing cell surface markers and protein expression. Genetic testing, including cytogenetic analysis and next-generation sequencing, can identify specific mutations and guide treatment. While blood tests do not diagnose lymphoma, they help assess organ function and provide prognostic information. Together, these methods allow for accurate diagnosis, staging, and treatment planning[17].

V. STAGING

The Ann Arbor staging system was originally developed in 1971 for Hodgkin Lymphoma, and was latterly adapted for non-Hodgkin lym-phoma. The Lugano classification system further modified staging by incorporating positronemission tomography/ computed tomography PET- CT) results to determine the staging of the lymphoma. PET- CT is used for fluorodeoxyglucose- avid Lymphoma subtypes, with symptoms alone being used for carrying the remaining subtypes. The new staging system incorporates two symptom- based classification A(absence of symptoms) and B(presence of fever, weight loss, and night sweats) for Hodgkin Lymphoma[18].

Table 5.1: Lugano Classificaton for staging Lymphoma

STAGES	DESCRIPTON OF DISEASE FROM PET/CT RESULT
I	Single nodal group or single extralymphatic lesion
II	Multiple nodal groups on same side of diaphragm or with limited contagious extralymphatic involvement
III	Multiple nodal groups on both side on diaphragm, may involve the spleen
IV	Non contagious extralymphatic involvement

VI. TREATMENT

6.1 Treatment of Hodgkin Lymphoma

Combination chemotherapy along with “involved field radiation therapy” is the most common treatment. Involved field radiation therapy uses high-energy rays to target the HL cells. Other parts of the body are protected to reduce harm to healthy cells. Chemotherapy without radiation therapy may be the treatment for patients with widespread Hodgkin lymphoma, fever, night sweats or weight loss. The treatment may last from six to 10 months.

Patients with nodular lymphocyte- predominant Hodgkin lymphoma (NLPHL) need different treatment than patient with other HL subtypes. NLPHL is slow- growing and close to 100 percent of patients see long- term survival. The treatment for cases with NLPHL is involved field radiation. Cases do respond to chemotherapy, but the complaint tends to come back more frequently after chemotherapy.

Stem cell transplantation is the another treatment method used for both Hodgkin and Non- Hodgkin Lymphoma and its subtypes. But there are various factors which determines need of stem cell transplantation in patents.These factors may include the patients disease, subtype, stage, other treatment received and the patient physical capability to have the transplant. While a stem
cell transplant isn't an option for every case. There are mainly two types of stemcell transplantation including autologous stem cell transplantation and allogenic stem cell transplantation[19].

Examples of some treatment approaches used in Hodgkin Lymphoma:

ABVD – Adriamycin (Doxorubicin), Bleomycin, Vinblastine and Dacarbazine

BEACOPP – Bleomycin, Etoposide, Adriamycin (doxorubicin), Cyclophosphamide, Oncovin (Vincristine), Procarbazine and Prednisone

Stanford V – Mechlorethamine, Doxorubicin, Vinblastine, Vincristine, Bleomycin, Etoposide and Prednisone Brentuximab vedotin

6.2 Treatment of Non -Hodgkin Lymphoma

There are various factors used to make a treatment plan for Non- Hodgkin Lymphoma including the type of NHL the stage and category of disease and overall patent health.

The types of treatment include :

Chemotherapy – the main type of treatment for NHL

Drug therapy –Rituximab and certain other drugs are used to treat some types of NHL

Radiation therapy – an important added treatment given along with chemotherapy for some types of NHL

Stem cell transplantation – a procedure used for some types of NHL

Combination drugs used to treat Non- Hodgkin Lymphoma :

R-CHOP: Rituximab, Cyclophosphamide, Hydroxydoxorubicin (doxorubicin), Oncovin (vincristine) and Prednisone
R-CVP or F-CVP: Rituxan or Fludarabine, plus Cyclophosphamide, Vincristine and Prednisone
R-HCVAD: Rituximab, Cyclophosphamide, Vincristine, Adriamycin (Doxorubicin) and Dexamethasone alternating with R-MTXAraC: Rituximab, Methotrexate, Cytarabine (ara-C)
B-R: Bendamustine (Treanda) and Rituximab[20].

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