

Large cell lymphoma

Introduction

Term **lymphoma** includes a wide variety of cancer arising from white blood cells (lymphoid cells/ lymphocytes) of the lymphatic system.

It is further broadly classified into Non Hodgkin Lymphoma (NHL) and Hodgkin lymphoma (HL).

NHL is a result of monoclonal expansion of lymphoid cells, mainly B cells (85% cases) with remaining cases of either T cell or NK cells. These cells show clonal proliferation and genetic translocations.

Large cell lymphomas (LCL) is a group of aggressive non-Hodgkin lymphomas (NHL) characterized by the presence of large malignant lymphoid cells .

This article aims to provide knowledge that will help to diagnose these cases early by recognizing their symptoms and asking for appropriate investigations, so that prompt treatment will help in recovery.

Large cell lymphoma (LCL)

So called based on comparison of their nuclear size with normal histiocyte (macrophage-15 μm) or if their nuclear diameter is twice the size of a normal resting small lymphocyte (which is normally 6-8 μm)

Types of Large Cell Lymphoma

Large cell lymphomas are classified according to the cell of origin, morphology, immunophenotype, and genetic abnormalities.

1. Diffuse Large B-Cell Lymphoma (DLBCL)

This is the most common and clinically important type, which constitutes approximately 30–40% of all non-Hodgkin lymphomas worldwide.

This type is aggressive and is further classified based on their immunophenotype.

Despite their aggressive nature, advances in diagnostic techniques and targeted therapies have significantly improved patient outcome.

It is characterized by diffuse proliferation of large B lymphocytes that replace the normal lymph node architecture.

Patients may present with rapidly enlarging lymph nodes or extranodal disease involving the gastrointestinal tract, brain, skin, bone, or testes.

2. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

PMBCL arises from thymic B cells and typically affects young adults, particularly women.

It presents as a rapidly enlarging mediastinal mass causing chest pain, cough, shortness of breath, or superior vena cava syndrome.

3. Anaplastic Large Cell Lymphoma (ALCL)

ALCL is a T-cell lymphoma characterized by large pleomorphic cells expressing CD30.

It is divided into:

ALK-positive ALCL (better prognosis)

ALK-negative ALCL (less favorable prognosis)

Patients often present with lymphadenopathy, fever, night sweats, and skin involvement.

ALCL that originates in skin is called primary cutaneous ALCL and is usually less aggressive and with less chances of metastasis to organs and lymph nodes.

4. High-Grade B-Cell Lymphoma

This aggressive subtype includes lymphomas with rearrangements involving MYC and BCL2 and/or BCL6 genes (double-hit or triple-hit lymphomas).

These tumors grow rapidly and require intensive chemotherapy.

Risk factors for large cell lymphoma

1.DLBCL is associated with few risk factors like:

HIV

Organ transplantation

Autoimmune conditions, such as systemic lupus erythematosus, rheumatoid arthritis

Chronic inflammation

ALCL is more common in males than females and in rare cases is associated with breast implants. Children and young adults are more likely to have ALK positive ALCL than older patients.

Other rare associations are with Epstein Barr virus (BBV), hepatitis B virus (HBV), Hepatitis C virus (HCV) and Human T cell lymphotropic (HTLV-1) virus infections

Clinical Presentation

Symptoms vary depending on the site and extent of disease.

Common clinical features include:

Painless enlargement of lymph nodes in the neck, axilla, or groin

Fever

Night sweats

Unexplained weight loss (B symptoms)

Fatigue

Loss of appetite

Abdominal pain or swelling

Chest pain, cough, or breathlessness due to mediastinal involvement

Neurological symptoms when the central nervous system is affected

Extranodal involvement occurs in approximately one-third of patients and may involve the stomach, intestines, skin, bones, kidneys, liver, or brain.

Diagnosis

Diagnosis requires correlation of clinical findings with pathological and laboratory investigations.

1. Clinical Examination

A detailed history and physical examination are performed to assess lymph node enlargement, organomegaly, and systemic symptoms.

2. Blood investigations

Complete blood count, PT, Serum LDH, β -2-microglobulin etc are tests which help to detect the abnormality.

3. Lymph Node Biopsy

Excisional biopsy is the gold standard for diagnosis. Histopathological examination shows diffuse sheets of large atypical lymphoid cells with prominent nucleoli and numerous mitotic figures.

4. Immunohistochemistry (IHC)

IHC helps determine the subtype by detecting characteristic markers:

CD20, CD19, CD79a (B-cell markers)

CD3 (T-cell marker)

CD30 (ALCL)

ALK protein (ALK-positive ALCL)

BCL2, BCL6, MYC, MUM1, and Ki-67

5. Flow Cytometry

Used to determine the immunophenotype and clonality of lymphoma cells.

6. Cytogenetic and Molecular Studies

Fluorescence in situ hybridization (FISH) and PCR identify chromosomal rearrangements involving MYC, BCL2, and BCL6, which have prognostic significance.

7. Imaging Studies

CT scan

PET-CT scan

MRI (when CNS involvement is suspected)

These studies determine disease stage and treatment response.

8. Bone Marrow Examination

Bone marrow aspiration and biopsy assess marrow involvement and help in staging.

Staging of Large cell lymphoma

Like other non Hodgkin lymphoma, large cell lymphoma is staged as per **Ann Arbor staging system or Lugano staging system**. The **Lugano staging system** is a simplified, modern modification of the older **Ann Arbor classification which** incorporates PET/CT scans to make staging more accurate and less invasive.

Stage I: Involvement of a **single lymph node region** or a **single extranodal site (IE)** without nodal involvement.

Stage II: Involvement of **two or more lymph node regions** on the same side of the diaphragm. It can also include localized extranodal involvement contiguous with a nodal site (IIE).

Stage III: Lymph node involvement on **both sides of the diaphragm**. This may include the spleen, or contiguous extranodal sites.

Stage IV: **Widespread/diffuse extranodal involvement** (e.g., in the liver, bone marrow, or lungs), regardless of lymph node status.

Treatment

Treatment depends on lymphoma subtype, stage, age, and overall health.

Chemotherapy

The standard treatment for DLBCL is the R-CHOP regimen, consisting of:

Rituximab

Cyclophosphamide

Doxorubicin

Vincristine

Prednisone

Targeted Therapy

Monoclonal antibodies and newer targeted agents improve outcomes, particularly in relapsed disease.

Radiotherapy

Radiation therapy is useful for localized disease or bulky tumors after chemotherapy.

Stem Cell Transplantation

Autologous stem cell transplantation is considered for relapsed or refractory lymphoma responding to salvage chemotherapy.

CAR T-Cell Therapy

For patients with relapsed or treatment-resistant large B-cell lymphoma, CAR T-cell therapy offers promising long-term remission by genetically modifying the patient's T cells to attack lymphoma cells.

Supportive Care

Supportive measures include infection prevention, blood transfusions when necessary, nutritional support, pain management, and psychosocial counseling.

Prognosis

The prognosis depends on age, stage, performance status, serum lactate dehydrogenase (LDH) levels, extranodal involvement, and molecular features. The International Prognostic Index (IPI) is widely used to predict outcomes. With modern immunochemotherapy, many patients with DLBCL achieve complete remission, and approximately 60–70% can be cured.

Conclusion

Large cell lymphoma are a group of aggressive but potentially curable group of lymphoid malignancies. Early diagnosis with aid of histopathology, immunohistochemistry, and molecular testing is essential for accurate classification and appropriate treatment. Advances in chemotherapy, targeted therapy, stem cell transplantation, and CAR T-cell therapy have significantly improved survival rates. Continued research into molecular genetics and personalized medicine is expected to further enhance treatment outcomes and quality of life for affected patients.

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