* ***Non-Hodgkin's lymphoma***

These are a large group of clonal lymphoid tumours, about 85% are of B cell origin and 15% of T or NK (natural killer) cell origin.

-They are characterized by an irregular pattern of spread and a significant proportion of patients develop extranodal disease.

- The aetiology of the majority of cases of non-Hodgkin lymphomas (NHL) is unknown although infectious agents are an important cause in particular subtypes

Table Infections associated with haemopoietic malignancies.

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| --- | --- | --- |
| **Infection** | **Organism** | **Tumour** |
| **Virus** | HTLV–1 | Adult T-cell leukaemia/lymphoma |
| Epstein–Barr virus | Burkitt and Hodgkin lymphomas; post-transplant lymphoproliferative disease (PTLD) |
| HHV–8 | Primary effusion lymphoma |
| HIV–1 | High-grade B-cell lymphoma, primary CNS lymphoma, Hodgkin lymphoma |
| Hepatitis C | Marginal zone lymphoma |
| **Bacteria** | Helicobacter pylori | Gastric lymphoma (mucosa-associated lymphoid tissue MALT) |
| **Protozoa** | Malaria | Burkitt lymphoma |

**Cell of origin:**

▪ B-cell lymphomas tend to mimic normal B cells at different stages of development.

▪ T-cell lymphomas resemble precursor T cells in bone marrow or thymus, or peripheral mature T cells.

**Classification of non-Hodgkin lymphoma:**

The lymphomas are classified within a group of mature B-cell and T-cell neoplasm.

For many years clinicians have subdivided lymphomas into low and high-grade disease.

-In general terms, the low grade disorders are relatively indolent, respond well to chemotherapy but are very difficult to cure whereas high-grade lymphomas are aggressive and need urgent treatment but are often curable.

**-Low grade lymphoma:** e.g.

Follicular lymphoma, mantle cell lymphoma.

-**High Grade Lymphoma**: e. g.

Diffuse Large B-Cell Lymphoma, Burkitt’s lymphoma

**The WHO Classification of lymphoid neoplasms**

The World Health Organization (WHO) classification of lymphoid neoplasms considers the morphology, cell of origin (determined by immunophenotyping), clinical features, and genotype (e.g., karyotype, presence of viral genomes) of each entity.

1. Hodgkin lymphoma.
2. Non-Hodgkin’s lymphoma
   1. Precursor B-cell neoplasms (neoplasms of immature B cells)
   2. Peripheral B-cell neoplasms (neoplasms of mature B cells)
   3. Precursor T-cell neoplasms (neoplasms of immature T cells)
   4. Peripheral T-cell and NK-cell neoplasms (neoplasms of mature T cells and NK cells)

**PERIPHERAL B-CELL NEOPLASMS**

1. Chronic lymphocytic leukemia/small lymphocytic lymphoma
2. B-cell prolymphocytic leukemia
3. Lymphoplasmacytic lymphoma
4. Splenic and nodal marginal zone lymphoma
5. Extranodal marginal zone lymphoma
6. Mantle cell lymphoma
7. Follicular lymphoma
8. Hairy cell leukemia
9. Plasmacytoma/plasma cell myeloma
10. Diffuse large B-cell lymphoma
11. Burkitt lymphoma

**PERIPHERAL T-CELL AND NK-CELL NEOPLASMS**

1. T-cell prolymphocytic leukemia
2. T-cell granular lymphocytic leukemia
3. Mycosis fungoides/Sézary syndrome
4. Peripheral T-cell lymphoma, unspecified
5. Anaplastic large-cell lymphoma
6. Angioimmunoblastic T-cell lymphoma
7. Enteropathy-type T-cell lymphoma
8. Panniculitis-like T-cell lymphoma
9. Hepatosplenic γδ T-cell lymphoma
10. Adult T-cell leukemia/lymphoma
11. Extranodal NK/T-cell lymphoma
12. Aggressive NK-cell leukemia

* **Some neoplasms are common and collectively make up the vast majority of lymphoid neoplasm (more than 90%),**

**these include**

1. Precursor B- and T-cell lymphoblastic leukemia/lymphoma—commonly called acute lymphoblastic leukemia (ALL)

2. Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL)

3. Follicular lymphoma

4. Mantle cell lymphoma

5. Extranodal marginal zone lymphoma

6. Diffuse large B-cell lymphomas

7. Burkitt’s lymphoma

8. Multiple myeloma and related plasma cell dyscrasias

9. Hodgkin lymphoma

**Clinical features of non-Hodgkin's lymphomas:**

1. *Superficial lymphadenopathy***:** asymmetric painless enlargementof lymph nodes in one or more peripheral lymph node regions.
2. *Constitutional symptoms* Fever, night sweats and weight loss occur less frequently than in Hodgkin's disease.
3. *Oropharyngeal involvement*.
4. *Features due to* anaemia, neutropenia or thrombocytopenia.
5. *Organs* involvement, the liver and spleen are often enlarged. The gastrointestinal tract is the most commonly involved extranodal site after the bone marrow. Also Skin, brain, testis or thyroid can be involved.

|  |  |
| --- | --- |
| **Clinical Differences Between Hodgkin and Non-Hodgkin Lymphomas:** | |
| **Hodgkin Lymphoma** | **Non-Hodgkin Lymphoma** |
| 1. More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic | 1.More frequent involvement of multiple peripheral nodes |
| 2. Orderly spread by contiguity | 2.Noncontiguous spread |
| 3. Mesenteric nodes and Waldeyer ring rarely involved | 3.Mesenteric nodes and Waldeyer ring commonly involved |
| 4. Extranodal involvement uncommon | 4. Extranodal involvement common |

**Investigations**

* **Histology**

Lymph node biopsy or of other involved tissue is the definitive investigation.

* Morphological examination is assisted by Immunophenotypic and genetic analysis.
* A fine needle aspiration may be performed to exclude another cause of lymphadenopathy (e.g.tuberculosis,carcinoma) but is not useful in establishing a diagnosis of lymphoma.
* **Laboratory investigations:** -

1. In advanced disease with marrow involvement, there may be anaemia, neutropenia or thrombocytopenia.
2. Lymphoma cells (e.g. mantle zone cells, ‘cleaved follicular lymphoma’ or ‘blast’ cells) may be found in the peripheral blood in some patients.
3. Trephine biopsy of marrow to see if there is bone marrow involvement.
4. Increase LDH and uric acid.
5. Immunoglobulin electrophoresis may reveal a paraprotein.

**■ Specific subtypes of non-Hodgkin's lymphoma:**

**● Low-grade non-Hodgkin's lymphoma:**

1. ***Follicular lymphoma:*** 40% of adult lymphomas. It is often characterized by a benign course for many years**.** It is associated with the t(14,18) translocation (fuses the *BCL2* gene to the IgH locus on chromosome 14 and leads to the inappropriate expression of BCL2 protein, which functions to prevent apoptosis.)

Follicular lymphoma occurs predominantly in older persons (rarely before age 20 years) and affects males and females equally.

The natural history is prolonged (median survival, 7-9 years), but follicular lymphoma is not easily curable, a feature that is common to most of the **indolent lymphoid malignancies**

1. ***Mantle cell lymphoma****:* it is associated with a t(11,14) translocation that results in over-expression of **cyclin D1.** It is of aggressive behavior.
2. ***Marginal zone lymphomas:***are typically extranodal.

Mucosa associated lymphoid tissue (MALT) lymphomas come into this category at sites such as the stomach or thyroid. Gastric MALT lymphoma is the most common form and is preceded by *Helicobacter (H.) pylori* infection.

1. ***Lymphocytic lymphomas:*** Lymphocytic lymphomas are closely related to CLL

**● High Grade Lymphoma:**

1. ***Diffuse Large B-Cell Lymphoma:***

It is the most common type of NHL lymphoma. It is considered as heterogeneous group of mature B cell tumors that share a similar large-cell morphology and aggressive clinical behavior.

Highly associated with rearrangements or mutations of BCL6 gene.

1. ***Burkitt's lymphoma*:** is one of the most highly proliferative subtypes of any tumours. It is associated with ***translocations of the* c-MYC *gene on chromosome 8*, as result of translocation (t(8;14)).**

Endemic (African) Burkitt's lymphoma is seen in areas with chronic malaria exposure and is associated with Epstein-Barr virus (EBV) infection. Typically, the patient, usually a child, presents with massive lymphadenopathy of the jaw which is initially very responsive to chemotherapy although long-term cure is uncommon

Sporadic cases may occur elsewhere in the world. It affects mainly children and adolescents, and has a greater tendency for involvement of the abdominal cavity (gastrointestinal tract, retroperitoneum, and ovaries) than the endemic form.

**◙ T-cell lymphoma** are less common and include: mycosis fungoides, peripheral T-cell lymphoma, anaplastic large cell lymphoma, enteropathy–associated T-cell lymphomas, and others.

**Clinical Staging of Hodgkin and Non-Hodgkin Lymphomas (Ann Arbor Classification)\***

|  |  |
| --- | --- |
| **Stage I** | Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or tissue (IE) |
| **Stage II** | Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited contiguous extralymphatic organs or tissue (IIE) |
| **Stage III** | Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS), limited contiguous extralymphatic organ or site (IIIE), or both (IIIES) |
| **Stage IV** | Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement |

---All stages are further divided on the basis of the absence (A) or presence (B) of the following systemic symptoms: significant fever, night sweats, unexplained loss of more than 10% of normal body weight.