Lymphoma

Introduction:

- The lifetime risk of developing non-Hodgkin lymphoma is 2.1% whereas the lifetime risk of developing Hodgkin lymphoma is considerably less
- The incidence has only slightly declined, death rate have decreased significantly owing to the improvements in treatment.
- The incidence of non-Hodgkin lymphoma rises with increased age whereas the incidence of Hodgkin lymphoma shows bimodal age distribution with early peak in 2^{nd} and 3^{rd} decades of life followed by sustained increase with older age

Cont. introduction:

- Although most of these cases seem sporadic, familial clustering can be seen
- Various viral infections are associated with increased risk
  - EBV is associated with Burkitt lymphoma, Hodgkin lymphoma
  - Human T-cell lymphotropic virus-1 associated with T-cell leukemia, lymphoma
  - Hepatitis C virus is associated with increased risk of lymphoma particularly splenic marginal zone lymphoma
  - HIV is associated with increased risk of B-cell lymphoma

Patients with autoimmune rheumatic disorders

Evaluation and Diagnosis:

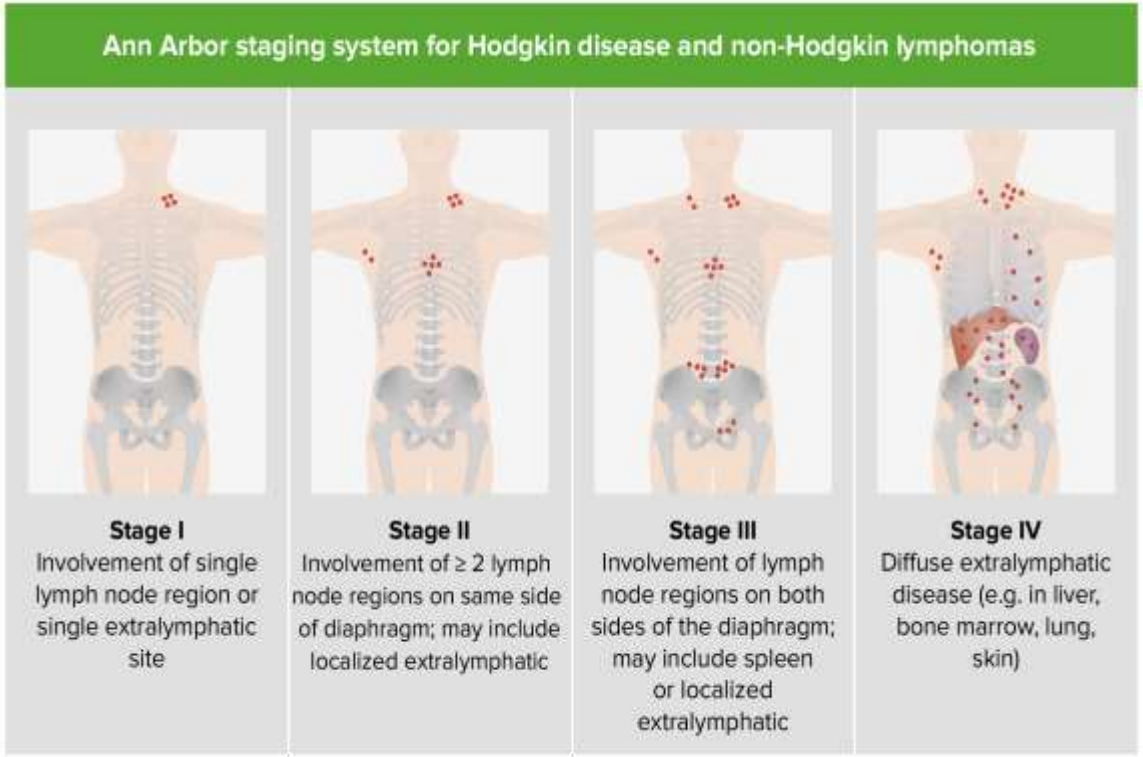
- Lymphadenopathy is the most common sign of lymphoma
- Other causes of lymphadenopathy (inflammatory, infectious) should be investigated
- Increase in size, distribution and persistence along with systemic symptoms raises the concern of lymphoma
- CT scan of the chest abdomen and pelvis to assess lymph nodes that are not amenable to physical examination
- Excisional biopsy is often preferable to core needle biopsy as it determine the nodal architecture
- Flow cytometry can suggest monoclonality and

Classifications:

- Diagnosis and classification of lymphoma are established not just on standard cell type and nodal architecture but also on flow cytometry, immunohistochemical stains and cytogenic and molecular genetic features
- There can be disagreements among experts and some overlap among tumor types

Staging:

- Staging the anatomical extent of spread can be simplified through the Ann Arbor staging system
- Staging involves physical examination, CT scan and PET scan in most patients
- Stages are also designated A (no systemic symptoms) or B (presence of one or more of: fever > 38, drenching night sweats, or weight loss of >10%



Non-Hodgkin Lymphoma

Approximately 85% of non-Hodgkin lymphomas are B-cell derived and express surface immunoglobulin and B-cell markers whereas 15% are t-cell derived

	Cell Line	
	B cell (90%)	**T cell (10%)**
Indolent	Follicular Lymphoma CCL / Small Lymphocytic Lymphoma Marginal Zone Lymphoma (MALT, Nodal, and Splenic variants)	Mycosis Fungoides
Aggressive	Diffuse Large B Cell Lymphoma (DLBCL) Mantle Cell Lymphoma	PTCL NOS Anaplastic Large Cell Lymphoma Angioimmunoblastic T Cell
Highly Aggressive	Burkitt Lymphoma	

Indolent B-cell lymphoma

Follicular Lymphoma:

This type of lymphoma demonstrate lymph node architecture with follicular morphology.

They arise from the germinal centre B cells of the lymph node

Characterized by the presence of a t(14;18) translocation that causes an overexpression of BCL2 oncogene.

They are classified based on their dominant cell type:

- grade 1: predominantly smaller cells
- grade 2: mixture of small and larger cells
- grade 3: predominantly large cells

Cont. Indolent B-cell lymphoma

For prognostic and treatment purposes grade 1 and 2 are commonly combined

Grade 3 is divided into grade 3A (more akin in behaviour and treatment to grade 1and 2), 3B (treated more like diffuse large B-cell lymphoma.)

It is the most common indolent lymphoma, accounts for 30% of non-Hodgkin lymphomas

Many patients are not symptomatic at diagnosis and may not require therapy for many years

Cont. Indolent B-cell lymphoma

- Because of its indolent nature, it is often diagnosed at an advanced stage, with splenic, hepatic involvement, and bone marrow involvement (stage III, IV)
- When therapy is indicated, single agent rituximab is associated with high response rates and durable remission
- Combining rituximab with chemotherapy (alkylating agents) leads to remission in more than 90% of patients
- Histologic transformation, most typically to a diffuse large B-cell lymphoma, occurs in 30% of patients and is associated with an aggressive course and poor prognosis

Cont. Indolent B-cell lymphoma

Mucosa-Associated Lymphoid Tissue Lymphoma (MALT lymphoma): is an extra nodal **marginal zone lymphoma**

Gastric MALT lymphoma is associated with Helicobacter pylori infection.

It can arise in other sites of the GI tract as well as in the thyroid, Orbits, skin, and lungs

H.Pylori associated malt is treated with PPI and antibiotics which will lead to remission

Other localized MALT lymphomas may be treated with irradiation

Cont. Indolent B-cell lymphoma

Small Lymphocytic Lymphoma (SLL)

SLL is considered to be the same disease as chronic lymphocytic leukemia (CLL) as they share the same genetic and molecular features. Notably, when the disease manifests in tissue or lymph nodes it is designated as SLL, while hematologic manifestations are classified as CLL

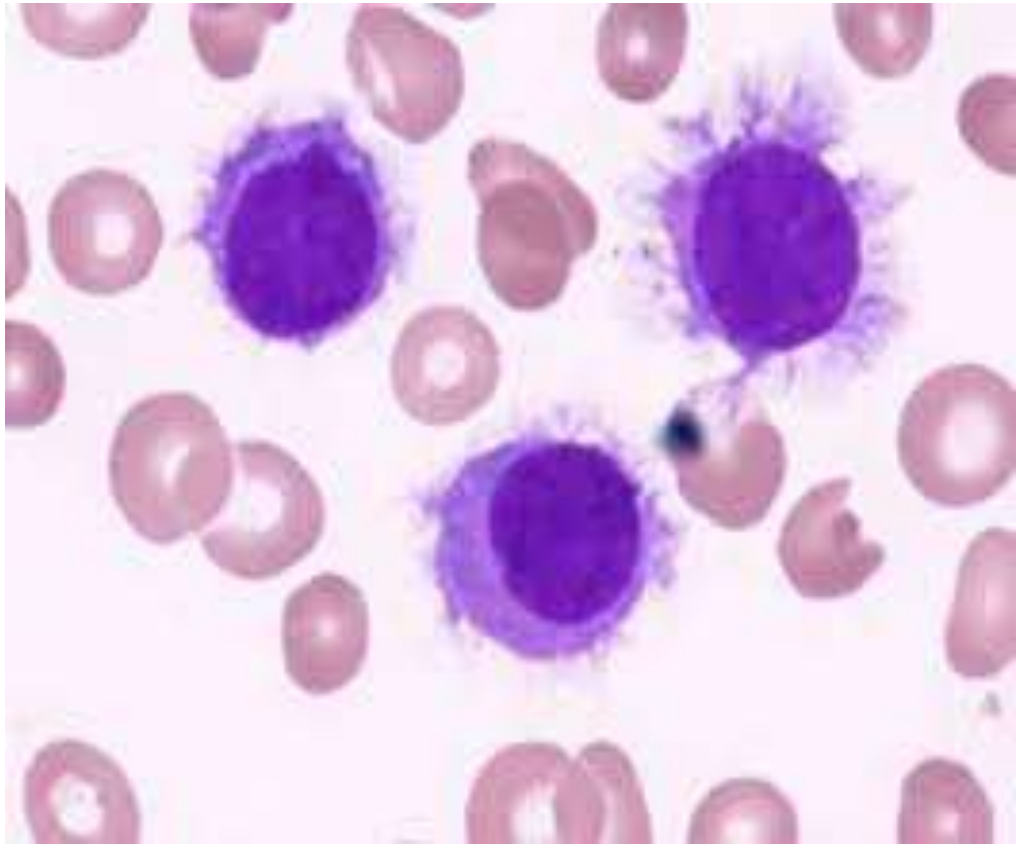
Cont. Indolent B-cell lymphoma

Hairy cell leukemia:

Is a low grade B-cell disorder with a characteristic clinical pathological, immunophenotypic and genetic changes.

Patients present with cytopenia and splenomegaly; LAP is typically absent

Circulating hairy cells are often identified in peripheral blood smear, when seen on bone marrow biopsy these cells have lacunar appearance



Cont. Indolent B-cell lymphoma

- Classically the bone marrow aspirate is a dry tap due to some degree of marrow fibrosis
- The BRAFV600E mutation has been associated with hairy cell leukemia in most patients and represents not only a diagnostic marker but also a therapeutic target.
- As with CLL/SLL some patients with hairy cell leukemia do not require treatment if not symptomatic
- However the front line therapy remain purine nucleoside agents.

Aggressive B-cell Lymphomas:

Diffuse Large B-cell Lymphoma:

They present 30% of non-Hodgkin lymphomas

Patients often present with symptomatic enlarging lymphadenopathy

Approximately 40% may have symptoms or signs of extra nodal disease and 1/3 have systemic B symptoms.

Biosy specimens show diffuse effacement of normal nodal architecture by large atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm.

Cont. aggressive B-cell lymphoma:

- 60% of patients have advanced (stage III or IV) disease at diagnosis
- Standard therapy is rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)
- Consolidative radiation therapy may be given to sites of bulky disease
- Patients who present with with localized disease can be treated with shorter course of chemotherapy with consolitave radiation therapy.

Cont. aggressive B-cell lymphoma:

Poor prognostic features:

- elevated LDH level
- extensive tumour burden
- poor performance status

Cont. aggressive B-cell lymphoma:

Mantle Cell Lymphoma:

It represent approximately 3-6% of non-Hodgkin lymphomas.

Median age at diagnosis is 68 years, and there is a 3:1 male predominance

It is defined by a t(11;14) translocation which leads to constitutive overexpression of cyclin D1, a cell-cycle gene regulator.

Patients can present with nodal or extra nodal disease, and the disease is usually widely disseminated at diagnosis

GI involvement with lymphomatoid polyposis is well described as is involvement of peripheral blood and bone marrow

This disease is responsive to various conventional

Cont. aggressive B-cell lymphoma:

Burkitt Lymphoma:

- A relatively rare lymphoma, and it is remarkable for its extremely rapid growth
- The endemic form occurs primarily in Africa, is a common cause of childhood cancer, and it is associated with EBV infection, it presents with large jaw mass
- The sporadic form is more typically seen in the developed world, occurs at somewhat later age and is more likely to present with abdominal or pelvic involvement
- MYC gene activation is characteristic of this lymphoma

Cont. aggressive B-cell lymphoma:

- Early signs of tumour lysis syndrome are often present in patients with Burkitt lymphoma even before treatment is initiated and should be anticipated during treatment because the tumour is quite chemosensitive
- Prophylaxis for TLS should be started before initiation of treatment
- Various aggressive multiagent chemotherapy regimens with rituximab have been associated with high cure rates

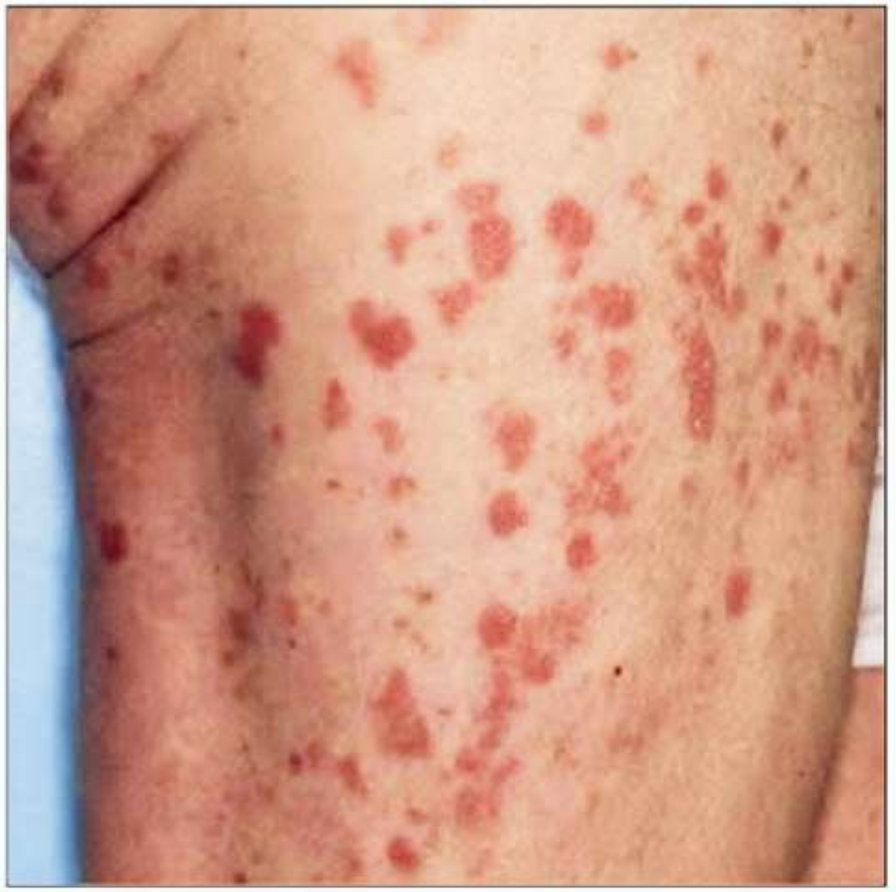
T-cell lymphomas:

- T- cell lymphomas, a heterogenous group of disorders with distinct clinical features and morphology, represent approximately 10-15% of lymphomas in Western countries but are more common in Asia.
- Diagnosis relies on routine pathology flow cytometry and immunohistochemistry.
- Monoclonality can be confirmed by findings of clonal rearrangements of the T-cell receptor genes detected by PCR
- In general, t-cell lymphomas are more refractory and relapse more quickly in response

Cont. T-cell lymphomas:

Cutaneous T-cell Lymphoma:

- Mycosis fungoides and Sezary syndrome are the two major subtypes of cutaneous T-cell lymphoma
- The skin findings in mycosis fungoides range from nonspecific macular-popular eruptions or plaques, to more defined skin



Cont. T-cell lymphomas:

- Pruritis is common and can be debilitating
- Ultimately as skin involvement becomes more extensive, the disease often progresses to involve extracutaneous sites including lymph nodes and organs (such as lung, liver and GI tract)
- Infections are more common as a function of underlying immunodeficiency and disruption of the protective barrier provided by healthy skin

Cont. T-cell lymphomas:

- Sezary syndrome is a more aggressive form of cutaneous T-cell lymphoma in which diffuse erythroderma characterizes the skin involvement and malignant t cells circulate in the blood
- Early stages of cutaneous T-cell lymphoma are confined to the skin and managed with topical therapy (steroids, retinoids, UV light) that may be combined with interferon (survival 10 years)
- More advanced disease is associated with survival of less than 4 years and requires more aggressive treatment with radiation and

Cont. T-cell lymphomas:

Anaplastic Large Cell lymphoma:

- Can present as nodal or extra nodal (skin, bone marrow and bone)
- Commonly have B symptoms
- Tumour cells are typically CD30 positive
- An important prognostic and potentially therapeutic distinction is the presence or absence of a t(2;5) or variant ALK gene translocation and protein expression
- Patients with ALK positive disease are younger and have more favourable prognosis with

Cont. T-cell lymphomas:

Angioimmunoblastic T-Cell Lymphoma:

- It was thought to be a disease of impaired immune regulation rather than a true malignancy
- They often present with systemic B symptoms, generalized LAP, hepatosplenomegaly, and skin rash
- Autoimmune manifestations such as AIHA may be present
- Although the lymphoma in some patients is responsive to glucocorticoids and conventional chemotherapy, it typically has a moderately aggressive clinical course and median survival of less than 2 years

Cont. T-cell lymphomas:

Lymphoblastic Lymphoma:

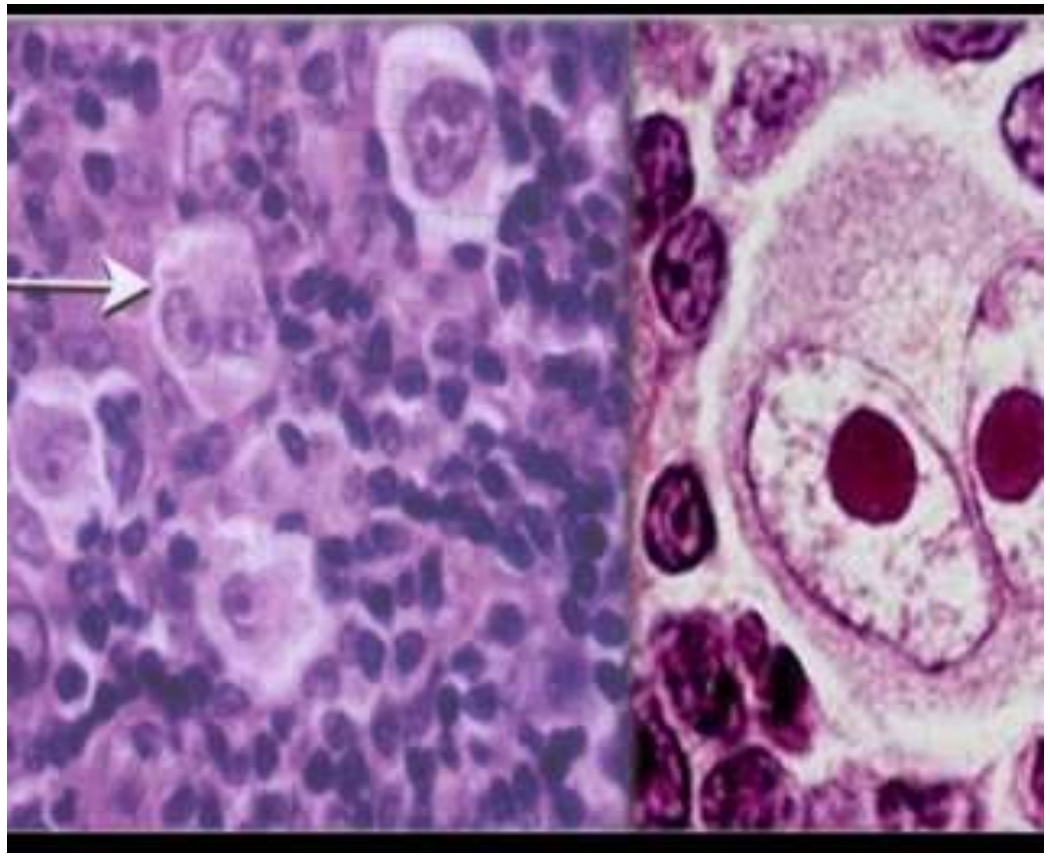
- It is an aggressive lymphoma that can be of T- or B- cell origin
- It is akin to and treated with protocols for acute lymphoblastic leukemia (ALL)
- Presentation with a mediastinal mass, blood or bone marrow and central nervous system involvement is typical

Hodgkin Lymphoma:

- Hodgkin lymphoma represents approximately 10% of lymphomas and is curable in most patients
- It most commonly presents in young adults
- Presentation with mediastinal, cervical and supraclavicular involvement is particularly common for the nodular sclerosing subtype
- Patients may also present with B symptoms, although that is more commonly seen in elderly patients with more advanced disease
- Pruritis may also be a presenting symptom

Cont. Hodgkin Lymphoma:

- Lymph node biopsy specimen shows Reed-Sternberg cells, malignant cells that originate from germinal centre B cells and are seen in an inflammatory infiltrate
- The number of reed-Sternberg cells and variability in the composition of the infiltrate lead to pathologic subtypes



Cont. Hodgkin Lymphoma:

- More than 90% of patients present with classic Hodgkin lymphoma pathology, and even with early stage disease, receive chemotherapy because this has been shown to result in higher cure rates.
- The doxorubicin, bleomycin, vinblastine, and dacarbazine regimen has been the most commonly used
- Fertility is better preserved and secondary acute leukemia less common
- Complete response indicated by PET scan after 2-3 cycles of chemotherapy is a reliable

Cont. Hodgkin Lymphoma:

- Nodular lymphocyte – predominant Hodgkin lymphoma is distinct clinically and pathologically from classic Hodgkin lymphoma (nodular sclerosis, mixed cellularity, and lymphocyte depleted)
- It represents approximately 10% of Hodgkin lymphomas and is more likely to present with localized disease but is associated with a high rate of late relapse
- Early stage disease may be treated with radiation therapy alone
- Single - agent rituximab or combined with

Thank you!