Lymphoid malignancy

- range from the most indolent to the most aggressive human malignancies.
- These cancers arise from cells of the immune system at different stages of differentiation, resulting in a wide range of morphologic, immunologic, and clinical findings
- Malignencies of lymphoid cell may present as Leukemia (primary involvement of bone marrow & blood),Lymphoma (solid tumor of immune system) or both.

Lymphoid malignancy

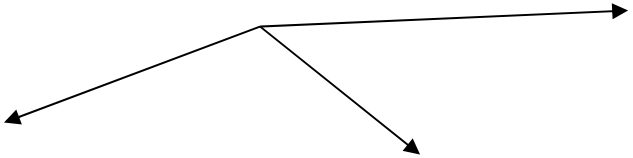
Etiology

- Inherited immunodeficiency disease
  - Klienfelters syndrome, ataxia telangiectasia, wiscott-aldrich syndrome, downs syndrome
- Acquired immunodeficiency disease
  - Iatrogenic immunosuppression, HIV, acquired hypogammaglobulinemia
- Autoimmune disease
  - Sjogrens disease, celiac disease, SLE, rheumatoid arthritis
- Chemical or drug exposure
  - Phenytoin, digoxin, radiation, chemotherapy

WHO Classification

- In 1999, the World Health Organization (WHO) classification of lymphoid malignancies was devised.
- The WHO classification takes into account morphologic, clinical, immunologic, and genetic information and attempts to divide non-Hodgkin's lymphomas and other lymphoid malignancies into clinical/pathologic entities that have clinical and therapeutic relevance.
- This system is clinically relevant and has a higher degree of diagnostic accuracy than those used previously.

WHO classification



Hodgkin´s disease

B cell

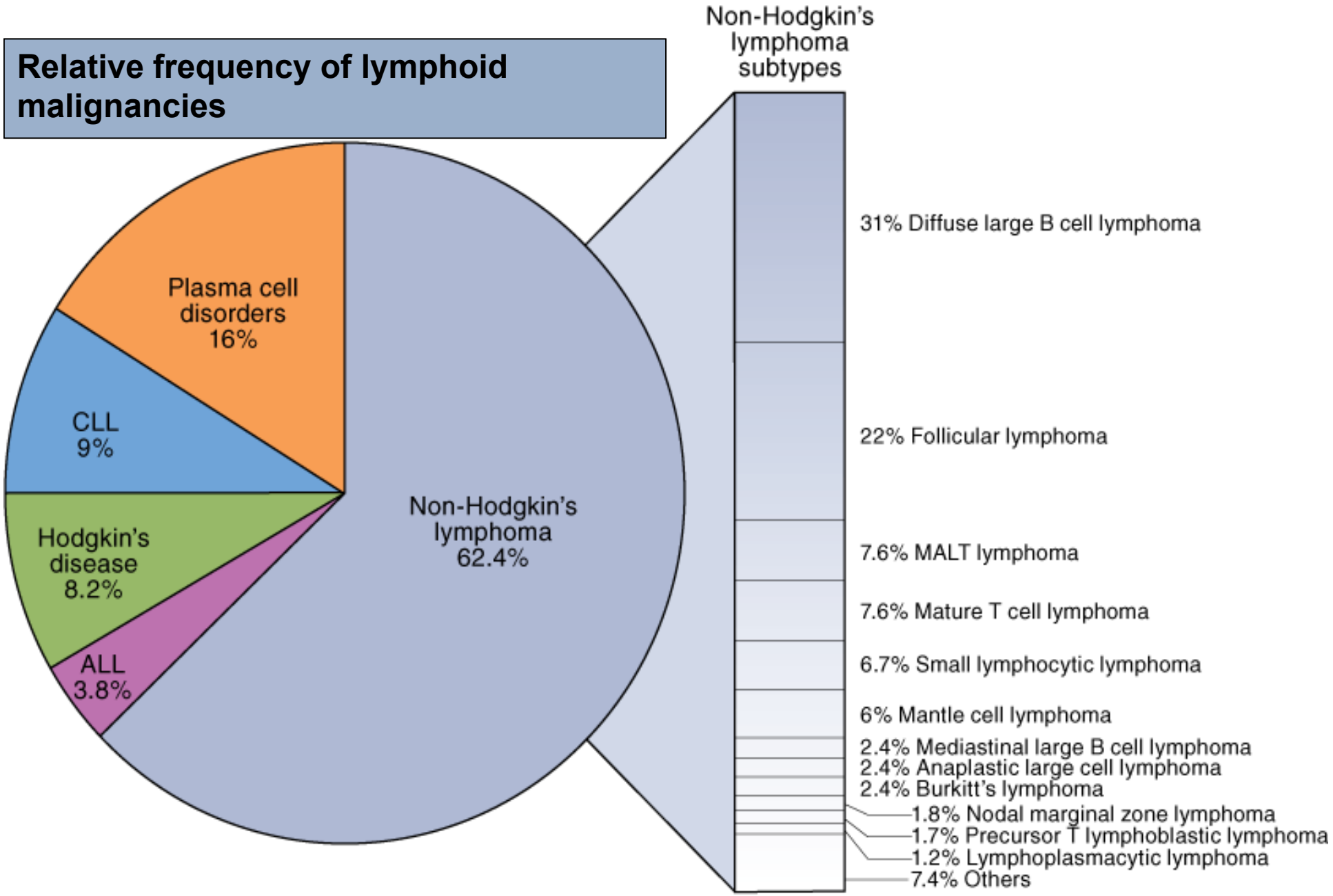
T cell

Precursor B cell neoplasm
- B cell ALL

Mature (peripheral) B cell neoplasm
- B cell CLL
- Hairy cell leukemia
- Plasma cell
  Myeloma / plasmacytoma
- Extranodal marginal zone
  B cell Lymphoma of MALT type
- Mantle cell lymphoma
- Follicular lymphoma
- Diffuse large B cell lymphoma
- Burkitt´s lymphoma

Precursor T cell neoplasm
- T cell ALL

Mature (peripheral) T cell neoplasm
- Mycosis fungoides / sezary syndrome
- Peripheral T cell lymphoma
- Anaplastic large cell lymphoma



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Infectious agents associated with lymphoid malignancy

agent	lymphoid malignancy
Epstein Barr virus	Burkitt´s lymphoma, post organ transplant lymphoma, hodgkin´s disease
HTLV -I	Adult T cell leukemia
HIV	Diffuse large B cell lymphoma Burkitt´s lymphoma
Hepatitis C virus	Lymphoplasmacytic lymphoma
H. pylori	Gastric MALT lymphoma
HSV-8	Primary effusion lymphoma, multicentric castleman´s disease

Pathogenesis

- All lymphoid cells are derived from a common hematopoietic progenitor that gives rise to lymphoid, myeloid, erythroid, monocyte, and megakaryocyte lineages.
- Through the ordered and sequential activation of a series of transcription factors, the cell first becomes committed to the lymphoid lineage and then gives rise to B and T cells.
- About 75% of all lymphoid leukemias and 90% of all lymphomas are of B cell origin.
- Malignancies of lymphoid cells are associated with recurring genetic abnormalities

Approach to the Patient

- careful history and physical examination.
- helps making the diagnosis, identify those manifestations of the disease that might require prompt attention, and aid in the selection of further studies to optimally characterize the patient's status to allow the best choice of therapy.

Evaluation for Non-Hodgkin's Lymphoma

- Physical examination
- Documentation of B symptoms
- Laboratory evaluation - CBC,LFT, Uric acid, Calcium
- Serum protein electrophoresis
- Serum $_2$-microglobulin
- Chest radiograph
- CT scan of abdomen, pelvis, and usually chest
- Bone marrow biopsy
- Lumbar puncture in lymphoblastic, Burkitt's, and diffuse large B cell lymphoma with positive marrow biopsy
- Gallium scan (SPECT) or PET scan in large cell lymphoma

Staging of Typical B Cell Lymphoid Leukemia

Stage	Clinical Features	Med.SY
RAI System		
Low risk	Lymphocytosis only in blood and marrow	>10
Intermediate	Lymphocytosis + lymphadenopathy + splenomegaly ± hepatomegaly	7
High	Lymphocytosis + thrombocytopenia +anemia	1.5
Binet System		
A	Fewer than three areas of clinical lymphadenopathy; no anemia or thrombocytopenia	>10
B	Three or more involved node areas; no anemia or thrombocytopenia	7
C	Hemoglobin 10 g/dL and/or platelets <100,000/L	2

The Ann Arbor Staging System for Hodgkin's Disease

Stage	Definition
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E" More than one extranodal deposit at any location Any involvement of liver or bone marrow
A	No Symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

International Prognostic Index for NHL

- Age> 60 years
- Serum lactate dehydrogenase levels elevated
- Performance status 2 (ECOG) or 70 (Karnofsky)
- Ann Arbor stage III or IV
- >1 site of extranodal involvement

Patients are grouped differently based upon the type of lymphoma e.g

For diffuse large B cell lymphoma

0, 1 factor = low risk

2 factors = low-intermediate risk

3 factors = high-intermediate risk

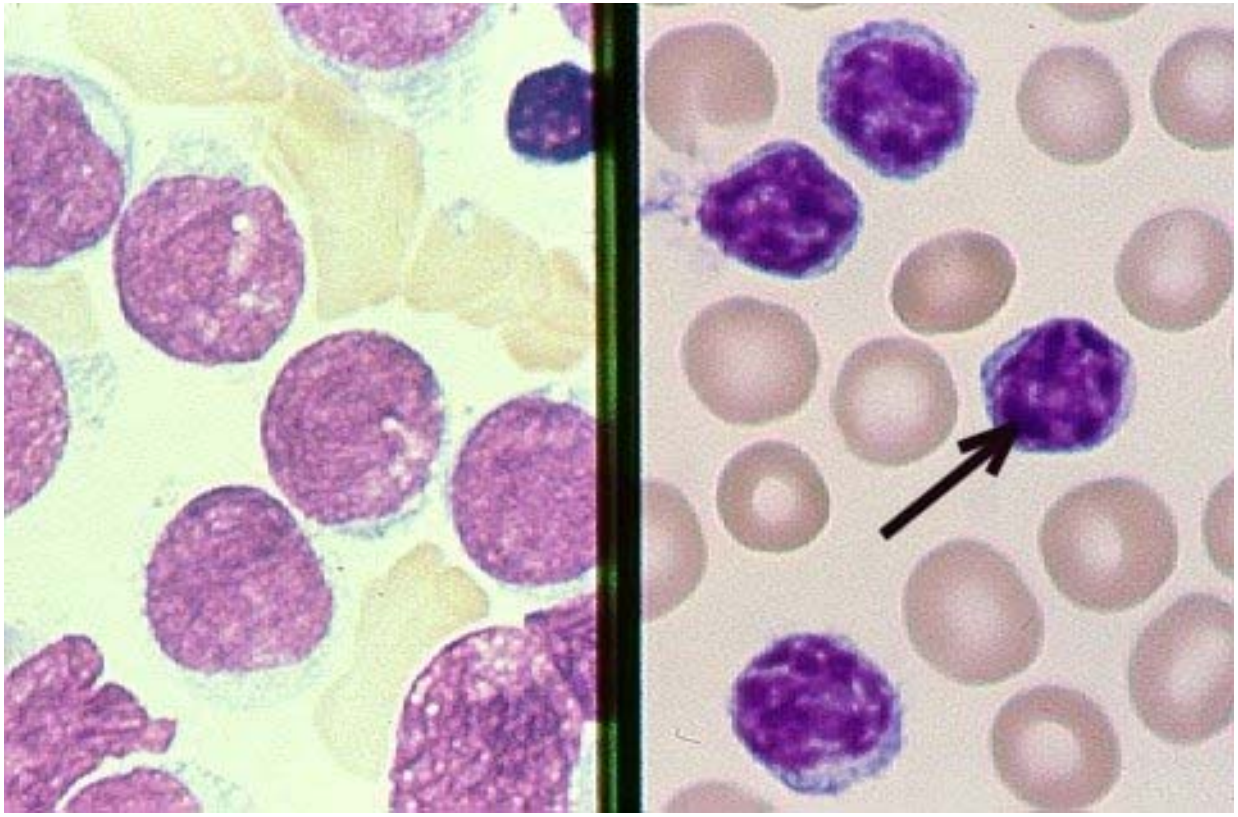
4, 5 factors = high risk:

ALL & CLL

- predominantly cancers of children and young adults
- L3 or Burkitt's leukemia occur in children in developing countries
- evaluation is usually completed after a complete blood count, chemistry studies reflecting major organ function, a bone marrow biopsy with genetic and immunologic studies, and a lumbar puncture

- most frequently in older adults and is exceedingly rare in children
- most prevalent form of leukemia in western countries
- complete blood count, chemistry tests to measure major organ function, serum protein electrophoresis, and a bone marrow biopsy.

ALL vs CLL



HL & NHL

- Determination of an accurate anatomic stage is an important part of the evaluation. The staging system is the Ann Arbor staging system originally developed for Hodgkin's disease

- Evaluation of patients with Hodgkin's disease will typically include a complete blood count; erythrocyte sedimentation rate; chemistry studies reflecting major organ function; CT scans of the chest, abdomen, and pelvis; and a bone marrow biopsy

HL & NHL

- In patients with non-Hodgkin's lymphoma, In addition, serum levels of lactate dehydrogenase (LDH) and beta $_2$-microglobulin and serum protein electrophoresis are often included in the evaluation.
- The prognosis of patients with non-Hodgkin's lymphoma is best assigned using the International Prognostic Index (IPI)

Hodgkin´s vs non hodgkin´s lymphoma

feature	Hodgkin´s	Non Hodgkin´s
Cell derivation	B cell mostly	90% B cell
Nodal involvement	Localized may spread to contiguous nodes	Disseminated nodal spread
Extra nodal spread	uncommon	common
Bone marrow involvement	uncommon	common
Constitutional symptoms	common	uncommon
Chromosomal defects	aneuploidy	Translocations, deletions
Spill over	never	May spread to blood
prognosis	75-85 % cure	30-40%

A/c lymphoblastic leukemia

Clinical feature - Anemia ,bleeding manifestation, fever, infection, pain &tenderness of bone, lymphadenopathy, splenomegaly, hepatomegaly, gum hypertrophy, meningeal involvement (↑ICT, FND), testicular enlargement.

Investigation –anemia, thrombocytopenia, WBC↑/↓,BF-smear cells, predominance of lymphoblast in blood & marrow. biochemistry, marrow biopsy with genetic and immunological studies, lumbar puncture (occult CNS involvement)

Classification of Acute Lymphoid Leukemia

Immunologic Subtype/ FAB Type	% case	Immuno typing	Cytogenetic abnormality
Pre-B ALL L1, L2 childhood ALL	75%	CD10+ 90%	t(9;22) t(4;11) t(1;19)
T cell ALL L1,L2 adult ALL	20%	CD10+ 30%	14q11 7q34
B cell ALL L3 Burkitt´s ALL	5%	CD10+ 50%	t(8;14) t(8;22) t(2;8)

Treatment

- Supportive treatment
- Allogenic SCT
- Chemotherapy

Induction - prednisolone(60mg/m2/d),
daunorubicin(20mg/m2/wk),
L-asparaginase(10,000u/m2/thrice/wk),
vincristine (1.5mg/m2/wk)

- Duration 4-6 wks
- Continue up to 8 wks if BM not N
- No response at 8 wks induction failure

Treatment cont.

Consolidation cyclophosphamide, L-asparaginase, Mtx, 6MP

CNS Prophylaxis

- Intrathecal Mtx wkly x 5-6 wks or
- Cranial irradiation 1800-2000 rads
- Triple intrathecal therapy – Mtx, hydrocortisone,ARA-C

Maintenance – 6MP , Mtx, Vincristine & prednisolone

Remission

- No leukemic cell
- ≤5% blast cell

Poor prognostic factors – WBC ≥100,000/Ul,male, age<2 or >10yrs, CNS involvement, L2 & L3 stage

Chronic lymphocytic leukemia

- Predominantly a disease of elderly
- M/F= 2:1
- Lymphoid malignancy of mature B cell

Clinical feature

Insidious onset, anemia, bleeding tendencies, recurrent infection, lymphadenopathy, splenomegaly, hepatomegaly

Investigation

- Anemia, marked leucytosis, platelet N or decreased,
- marrow -↑ lymphocyte, ↓myeloid & erythroid precursors,
- Biochemistry including LDH and **β** $_2$-microglobulin
- serum protein electrophoresis.

Other test

- Erythrocyte rosette test positive >90%
- Serum immunoglobulin decreased
- Coombs test positive -20% cases
- Positive pan B cell markers CD19,CD20,CD23

Treatment

- Degree of lymphocytosis is not an indication to initiate therapy
- Treatment started when patient is symptomatic with lymphadenopathy & hepato splenomegaly

Supportive treatment

Chemotherapy

- Chlorambucil oral 2-3 mg/kg/d x5d/wk x every 3wk
- Cyclophosphamide i/v 600 mg/m2 every 3-4 wk
- **Fludarabin** i/v 25-30 mg/m2/d x 5d every 4 wk
- Cladribine i/v 0.2mg/kg/d x 7d every 4wk
- Rituximab 75-500 mg/m2
- Bendamustine

Diffuse large B cell lymphoma

- Most common comprising 31% of NHL
- Median age of presentation 64yrs
- >50% of patient have some site of extra nodal involvement at diagnosis
- Diagnosis – biopsy evaluation by expert hematopathologist

Treatment

chemotherapy ± radiotherapy

- CHOP + Rituximab

(cyclophosphamide,hydroxydaunorubicin,vincristine(oncovin),prednisolone)

- SCT
- 5yrs survival 46%

Follicular lymphoma

- 22% of NHL
- Median age of presentation 59 yrs
- Diagnosis – biopsy evaluation by expert hematologist. confirmation B cell immunophenotype with t(14;18)

Treatment

- Localized follicular lymphoma –field radiotherapy –excellent result
- 25% undergo spontaneous remission
- Chloramphenicol /cyclophosphamide
  + CVP/R-CHOP most frequently used
- 50-75% achieve a complete remission
- Other agent used ; fludaribine, interferon,rituximab & lymphoma vaccine
- 5yr survival 72%

Extra nodal marginal zone B cell Lymphoma of MALT type

- Comprise 8% of NHL
- Median age of presentation 60 yrs
- Most frequent is gastric lymphoma of MALT type associated with H. pylori
- Diagnosis – biopsy from lymph node characteristic pattern of infiltration of small lymphocytes that are monoclonal B cells & CD5 negative

Treatment

- Curable when localized –surgery, radiation
- gastric MALT lymphoma infected with H. pylori can achieve remission (majority) with eradication of infection
- Extensive disease –chemotherapy (chlorambucil)

Mantle cell lymphoma

- 6% of NHL
- Median age of presentation 63yrs
- 74% male
- Diagnosis – biopsy of lymph node
- Approximately 70% are diagnosed at stage IV
- GIT involvement is common (waldeyer´s ring)
- CD5 positive

Treatment

- Combination therapy –chemotherapy+ radiotherapy –
  CHOP + Rituximab
  or hyperCVAD + Rituximab
- Fludarabin/+cyclophosphamide+mitroxantrone+R
- PEP-C (prednisone,etoposide,procarbazine)
- Targeted therapy –bortezomib,temsirolimus,Ibrutinib

Burkitt´s lymphoma

- ~30% childhood NHL-L3 type ALL
- Diagnosis – biopsy of lymph node
- 3 distinct clinical forms
  - Endemic- African children (jaw tumor)
  - Sporadic- western countries
  - Immunodeficiency associated –HIV
- Most rapidly progressive human tumor so prompt diagnosis & treatment necessary

Treatment

- Intensive chemotherapy high dose cyclophosphamide
- dose-adjusted EPOCH with Rituximab
- Prophylactic therapy to CNS is mandatory
- Cure 70-80 % of both children & young adult when effective therapy is administered precisely

Hairy cell leukemia

- Rare disease of older males
- Presentation involve pancytopenia, splenomegaly
- Malignant cells have hairy projections on light & electron microscopy & show characteristic staining pattern with tartrate resistant acid phosphatase
- Marrow aspirate dry tap, biopsy pattern is fibrosis with diffuse infiltration by malignant cells
- Complications – vasculitis, frequent infections

Treatment

- Cladribine – CR occurs in majority of patients (long term disease free survival is frequent)
- Pentostatin
- Rituximab
- Interferon α

Mycosis fungoides / sezary syndrome

- Cutaneous T cell lymphoma (often seen by dermatologist)
- Median age of presentation 55yrs
- Common in black males
- Indolent lymphoma ,often patient has several years of eczematous or dermatitic skin lesions before diagnosis is established
- sezary syndrome – lymphoma with erythroderma & circulating tumor cells

Treatment

- Radiotherapy
- Topical glucocorticoids
- Topical nitrogen mustard
- Phototherapy, interferon, antibiotics, fusitoxins
- Systemic cytotoxic therapy

Hodgkin´s disease

- Primarily arises within lymph nodes & involve extranodal sites
- Incidence bimodal peaks young adults 15-35 & >50yrs. M>F

Clinical feature

- Most patients present with palpable nontender lymphadenopathy around neck, supraclavicular,axilla & mediastinal adenopathy
- Fever (Pel Ebstein)
- Sever itching, cutaneous disorder (erythema nodosum), ichthyosiform atrophy, paraneoplastic cerebellar degeneration
- Nephrotic syndrome, immunehemolytic anemia, thrombocytopenia, hypercalacemia
- Pain in lymph node on alcohol ingestion
- Splenomegaly, hepatomegaly
- Constitutional symptoms(25-40%) type B symptoms (low grade fever >38 C, Night sweats –hypermetabolic state, wt.loss >10% x 6 m)
- Others - fatigue, malaise,weakness

staging evaluation of lymphoma

- Physical examination
- Documentation of B symptoms
- Lab – CBC, LFT,uric acid, calcium,serum protein electrophoresis, serum β2 microglobin, CXR,CT abdomen, pelvis, chest,bone marrow biopsy, LP,PET scan in large cell lymphoma
- Diagnosis – biopsy from lymph node, occasionally from other tissue & identification of reedsternberg cell

Modified Rye classification of HD

Histology	incidence	pathology	prognosis	RS cell
Lymphocytic Predominant	5	Proliferating few histiocytic	excellent	Few classic & polypoid
Nodular sclerosis	70	Lymphoid nodules collagen band	V. good	Freq lacunar
Mixed cellularity	22	Mixed infiltrate	good	Numerous classic
Lymphocytic depletion	1	Scanty lymphocytes atypical fibrosis	poor	Numerous pleomorphic

Treatment

- Localized HD cure >90% -extended field radiotherapy

- Radiotherapy stage I & IIA & lesion causing pressure complications
- Allogenic / autologous SCT
- Chemotherapy –
- ABVD (doxorubicin, bleomycin,vinblastin,dacarbazine)
- MOPP (mechlorethamine,vincristine,procarbazine,prednisolone)
- Prognosis 5 yrs survival IA >90% & IIA >70%