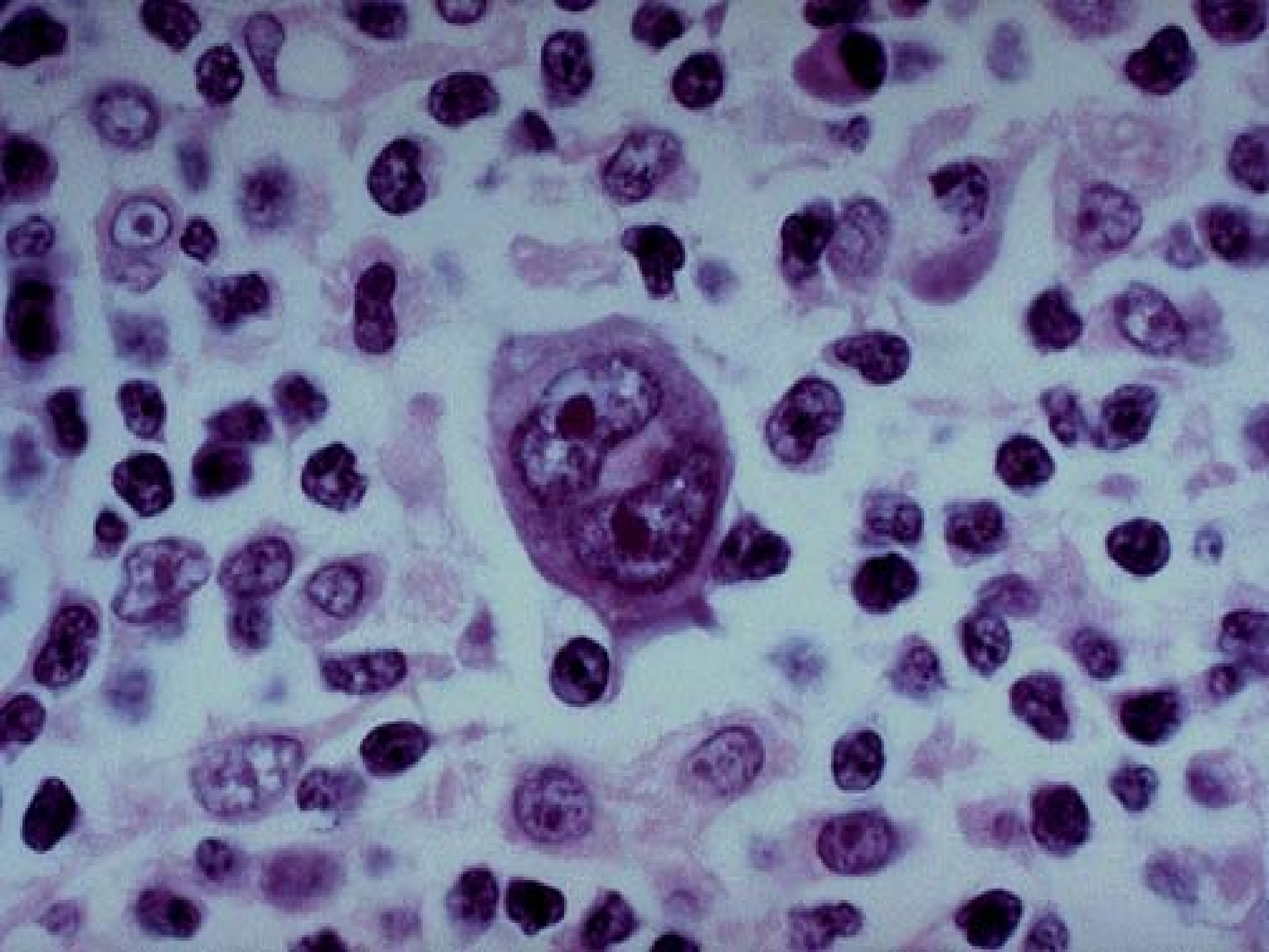
LYMPHOMAS



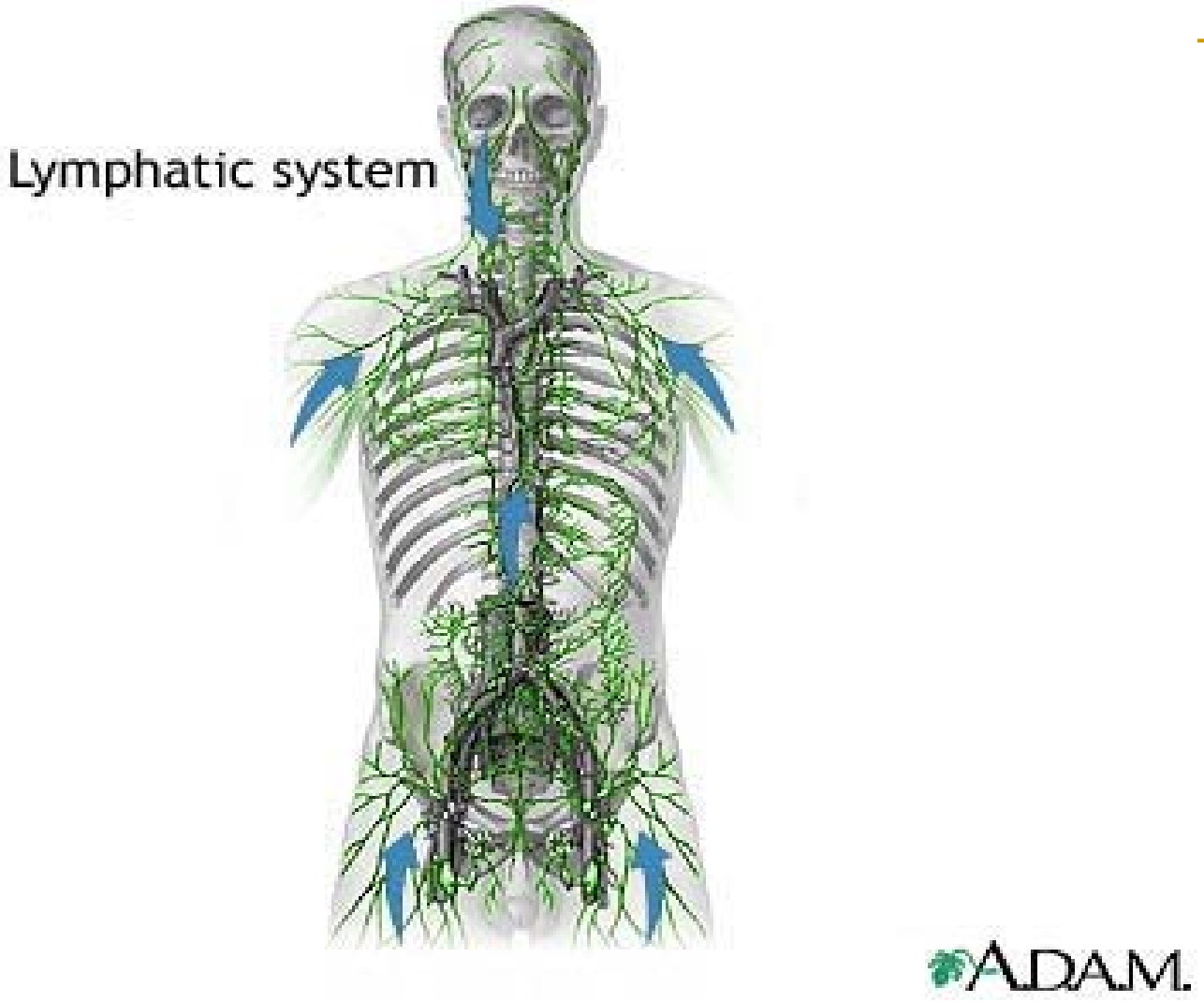
INTRODUCTION

- Lymphoma is a neoplasm of lymph tissue that is usually malignant. It can also be called Lymphadenoma.

- Lymphomas constitute a part of lymphoid neoplasms. Lymphoid neoplasms in turn include lymphocytic leukemias alongwith lymphomas.

- Lymphoid leukemias and malignant lymphomas are malignant counterparts of normal lymphoid cells at distinct stages of differentiation.*

* Blood 1995; 85:307



LYMPHATIC SYSTEM

INTRODUCTION

- The line between the lymphocytic leukemias and the lymphomas often blurs.
- Many types of lymphoma occasionally present with a leukemic peripheral blood picture accompanied by extensive marrow involvement, and evolution to leukemia is not unusual with progression of incurable lymphomas.
- Conversely, tumors identical to leukemias sometimes arise as lymphomatous masses without evidence of bone marrow disease. In addition, the clinical pattern can change over the course of illness.

Robbin's Path. Basis Dis. [6th Ed.]

INCIDENCE & MORTALITY OF LYMPHOMAS

	Males	Females
Incidence	5 %	4 %
Deaths	5 %	5 %

CA Cancer J Clin 1996; 46: 5

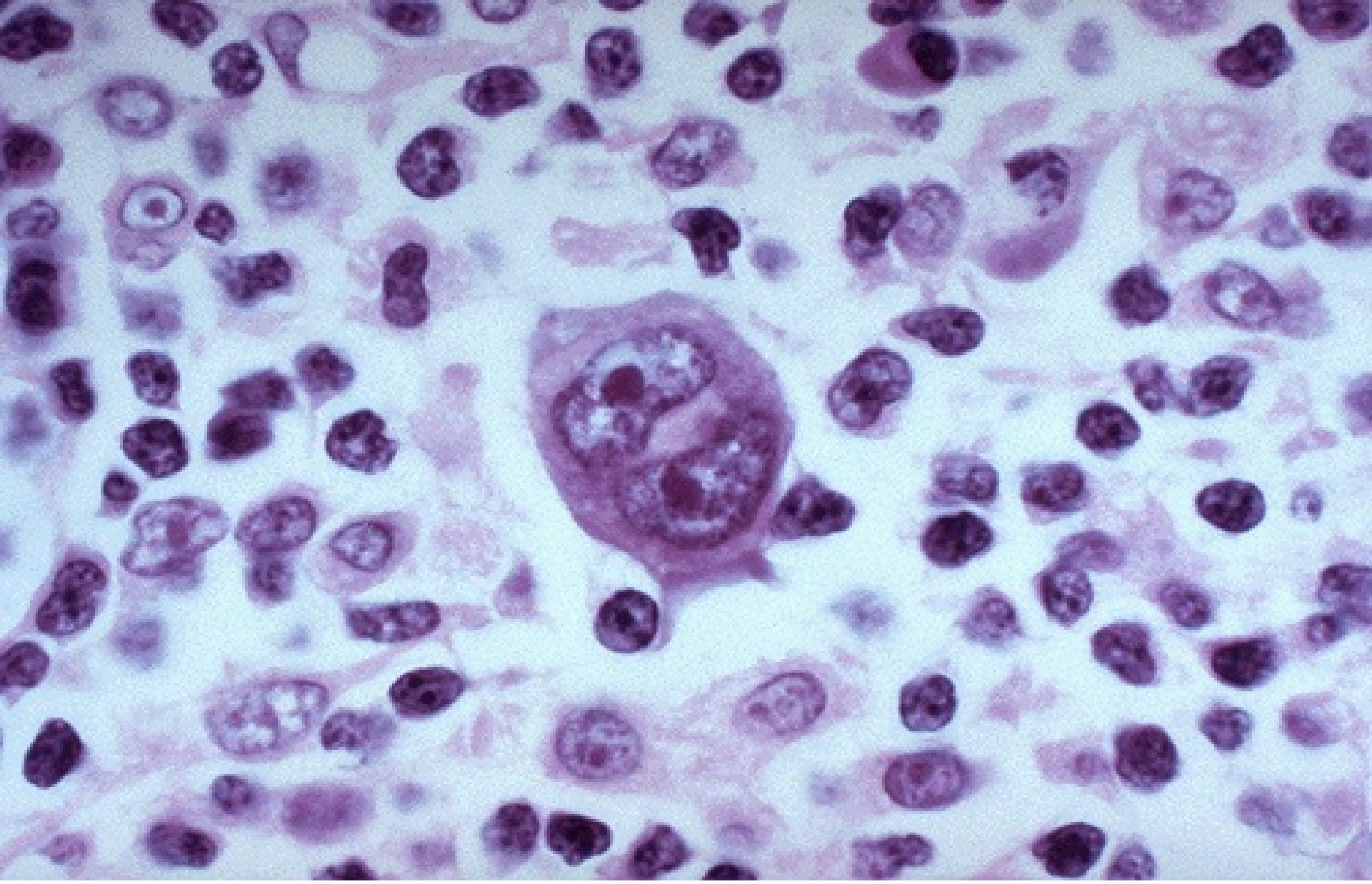
TYPES

On the basis of presence or absence of **Reed-Sternberg** cell, lymphoma have been divided into:

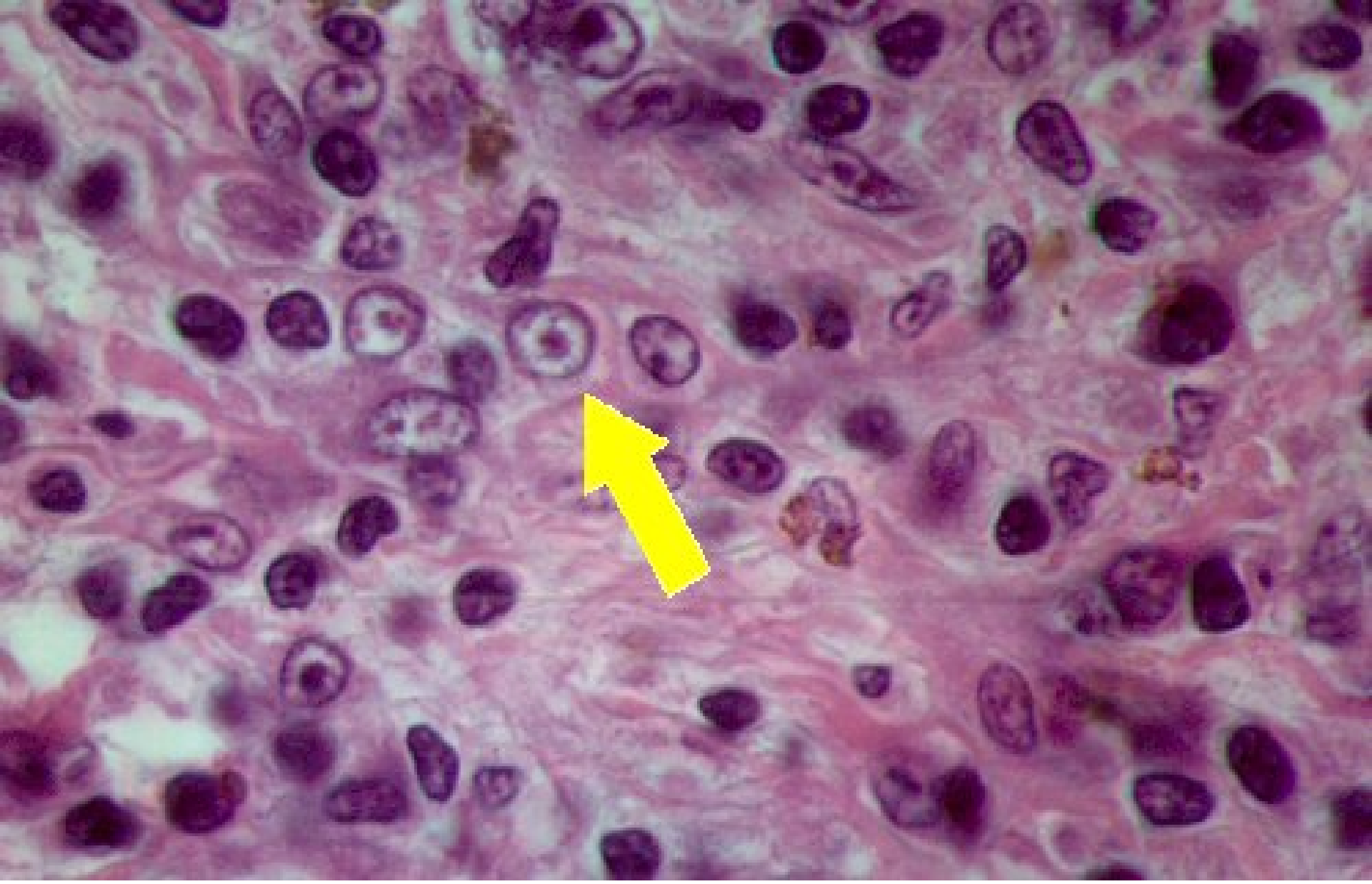
1. Hodgkin's Lymphoma (Hodgkin's disease)

2. Non Hodgkin's lymphoma

Curr Med Diag Treat 2004



REED STERNBERG CELL



LACUNAR CELL

EPIDEMIOLOGY

Hodgkin's disease

- About 8000 new cases are diagnosed annually in US.
- Age-specific incidence curve is bimodal with I peak in 15 to 35 years & II peak in people > 50 yrs of age.
- Most prevalent in males and that too in young adults.

Non-Hodgkin's lymphoma

- 45000 (6 times of Hodgkin's lymphoma)
- Incidence increases with age
- More prevalent in males.

Harrison's Prin Int Med [15th Ed]

EPIDEMIOLOGY

The increased prevalence of lymphomas in male patients has led some investigators to hypothesize a sex-linked genetic or hormonally related increase in susceptibility.

Harrison’s Prin Int Med [15th Ed]

ETIOLOGY / RISK FACTORS

Hodgkin's disease

Increased risk of Hodgkin's disease has been associated with:

- Decreased number of siblings
- Single family dwellings.
- Decreased number of playmates
- Early birth order
- A sibling with Hodgkin's disease
- Tonsillectomy
- In an identical twin of an affected case (99 fold)

ETIOLOGY / RISK FACTORS

Hodgkin's disease

- There is a strong evidence for a role of EBV in the pathogenesis of a subset of cases.
- Also there is an increased risk of Hodgkin's disease in patients with immuno-deficiencies and auto-immune diseases.

ETIOLOGY / RISK FACTORS

Non-Hodgkin's lymphoma

Infectious agents

- EBV has a strong association with development of Burkitt's lymphoma, some lymphomas associated with immunodeficiency including HIV 1 related lymphoma; and angiocentric lymphomas.
- HTLV 1 is the causative agent of the adult T-cell leukemia / lymphoma.
- Gastric MALT lymphoma occurs as a consequence of *Helicobacter pylori* infection.

ETIOLOGY / RISK FACTORS

Non-Hodgkin's lymphoma

- Diseases of inherited & acquired immunodeficiency as well as auto-immune diseases are associated with an increased incidence of lymphoma.
- Drug induced immunosuppression
- Acquired or congenital immunodeficiency.

ETIOLOGY / RISK FACTORS

Non-Hodgkin's lymphoma

- Chemical or drug exposure
  - Phenytoin
  - Digoxin, Phenoxybarbiturates
  - Pesticides
  - Hair dyes
  - Prior chemotherapy
- Radiation exposure, prior radiotherapy.

CLASSIFICATION

Hodgkin's disease

Hodgkin's disease has been classified into 2 main subgroups:

A. *Nodular lymphocyte- predominant Hodgkin's disease*

- Patients in this subset have a nodular growth pattern and a distinct clinical course.
- It represents < 5% of cases of Hodgkin's disease
- It is an unusual clinical entity.

CLASSIFICATION

B. Classical Hodgkin's disease

It is further divided into 4 histologic groups:

B.1 Lymphocyte predominant

- Uncommon (2-10%)
- Diffuse lymphocytic infiltrates with few Reed Sternberg cells
- Has excellent prognosis

B.2 Nodular sclerosis

- Most common form (70%)
- Fibrosis with collagen bands
- Frequent lacunar variants are seen
- More common in women.
- Excellent Prognosis

CLASSIFICATION

B. Classical Hodgkin's disease

B.3 Mixed Cellularity

- Common (20-40%)
- Numerous Reed Sternberg cells
- Pleomorphic infiltrates are seen
- Often presents with disseminated disease

B.4 Lymphocyte depleted

- Rare (2%)
- Numerous often bizarre Reed Sternberg cells seen with paucity of lymphocytes
- Aggressive clinically.

CLASSIFICATION

Non-Hodgkin's lymphoma

- REAL (Revised European American Classification of Lymphoma)
- Working Formulation of Clinical Usage
- Modified Kiel classification
- Rappaport terminology

CLASSIFICATION

Non-Hodgkin's lymphoma

The latest classification given by WHO divided NHL into 4 main categories:

A. Precursor B cell lymphomas

A.1 Precursor B lymphoblastic lymphoma

B. Peripheral (mature) B cell neoplasms

B.1 Small lymphocytic lymphoma

B.2 Lymphoplasmacytic lymphoma

B.3 Splenic marginal zone B cell lymphoma

B.4 Extranodal marginal zone B cell lymphoma of MALT type

CLASSIFICATION

B. Peripheral (mature) B cell neoplasms

B.5 Mantle Cell lymphoma
B.6 Follicular lymphoma
B.7 Nodal marginal zone B cell lymphoma
B.8 Diffuse large B cell lymphoma
B.9 Burkitt's lymphoma

C.Precursor T cell neoplasm

Precursor T cell lymphoblastic lymphoma

CLASSIFICATION

D. Peripheral (mature) T cell neoplasm

D.1 Extranodal NK/T cell lymphoma, nasal type
D.2 Enteropathy type T cell lymphoma
D.3 Hepatosplenic Gamma delta T cell lymphoma
D.4 Subcutaneous panniculitis like T cell lymphoma
D.5 Mycosis fungoides/ Sezary syndrome
D.6 Anaplastic large cell lymphoma, primary cutaneous type
D.7 Peripheral T cell lymphoma, not otherwise specified (NOS)
D.8 Angioimmunoblastic T cell lymphoma
D.9 Anaplastic large cell lymphoma, primary systemic type

CLINICAL FEATURES

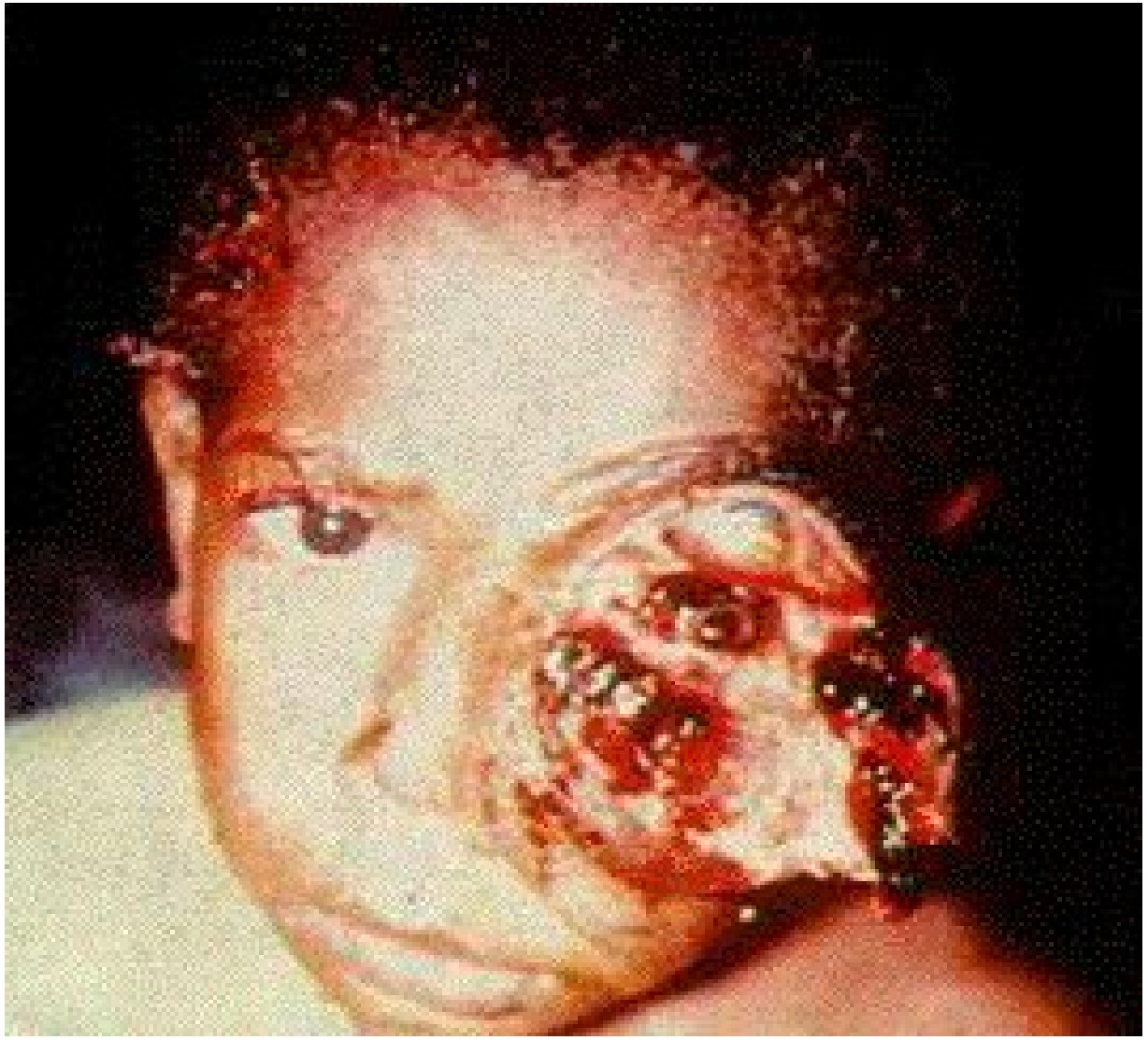
Hodgkin's disease

Lymphadenopathy

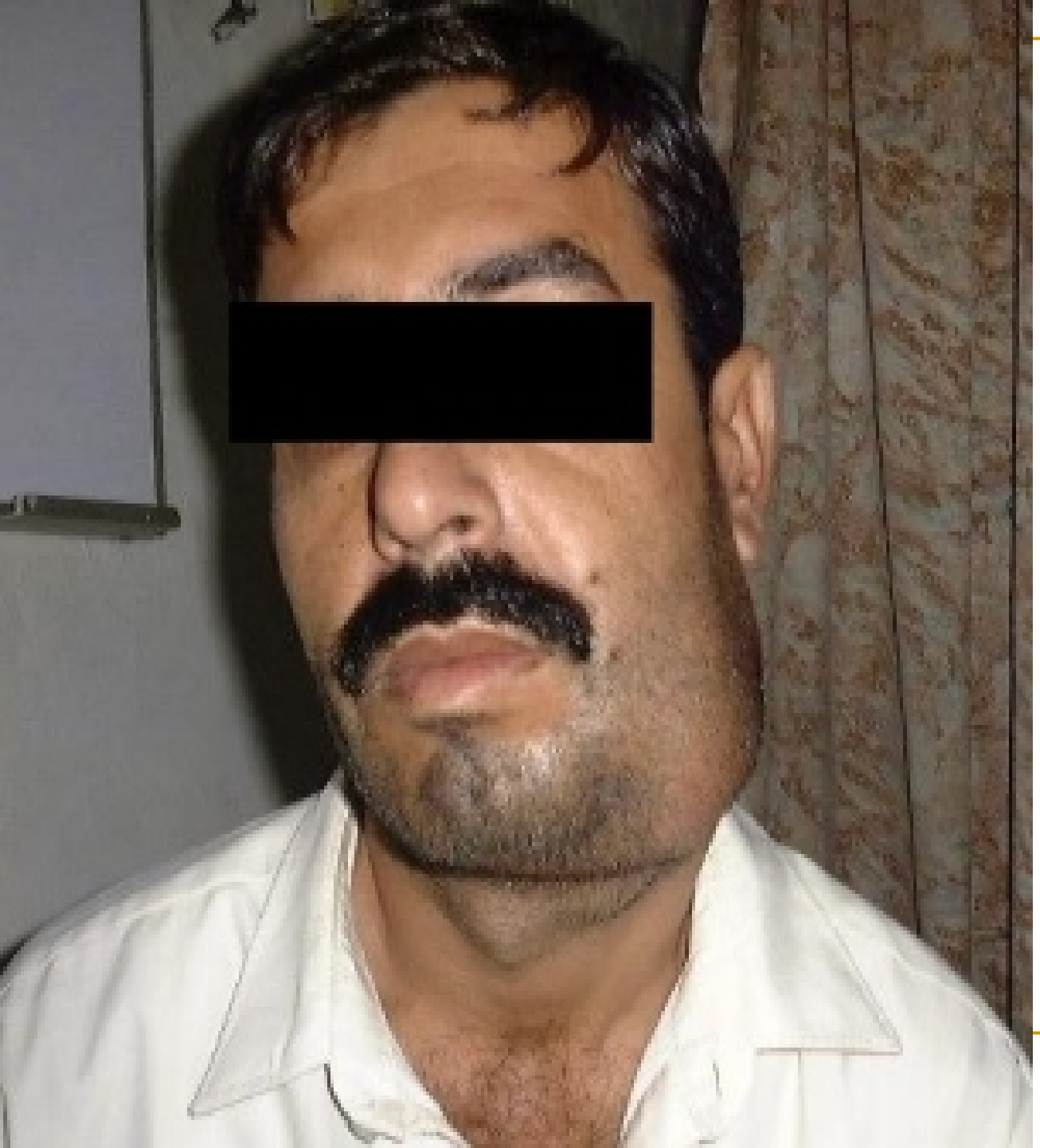
- Usually presents as a localized disease, subsequently spreads to contiguous lymphoid structures; ultimately disseminates to non-lymphoid tissues.

- Involves single or group of lymph nodes that are firm, freely moveable and usually non tender.

- About 50% patients present with adenopathy in the neck or supraclavicular area and over 70% of patients present with superficial lymph node enlargement.



An African male of age 9 years with Burkitt's lymphoma



A man aged 32 with Hodgkin’s lymphoma involving cervical lymph nodes.

CLINICAL FEATURES

Hodgkin's disease

Lymphadenopathy

- About 60% of patients present with mediastinal adenpathy (which is sometimes first detected on a routine chest X-ray)
- Node involvement tends to be centripetal or axial.
- Characteristically, lymph nodes or other tissues involved can become painful after the ingestion of alcoholic beverages.

CLINICAL FEATURES

Hodgkin's disease

Fever

- Generally low- grade
- Associated with recurrent night sweats.
- **Pel-Ebstein** fever: lasts 3-10 days followed by an afebrile period of 3-10 days.

Weight loss

- Unexplained weight loss of greater than 10% over 6 months or less.

CLINICAL FEATURES

Hodgkin's disease

Other symptoms include:

- Malaise
- Weakness
- Pruritus / skin rash
- Mediastinal, pleural, pulmonary or pericardial involvement may be associated with cough, chest pain, shortness of breath, or hypertrophic osteoarthropathy
- Bone involvement may be associated with bone pain.
- Obstruction of SVC.
- Sudden spinal cord compression
- Headache or visual disturbance (rare)
- Abdominal involvement may result in abdominal pain, bowel disturbances and even ascites.

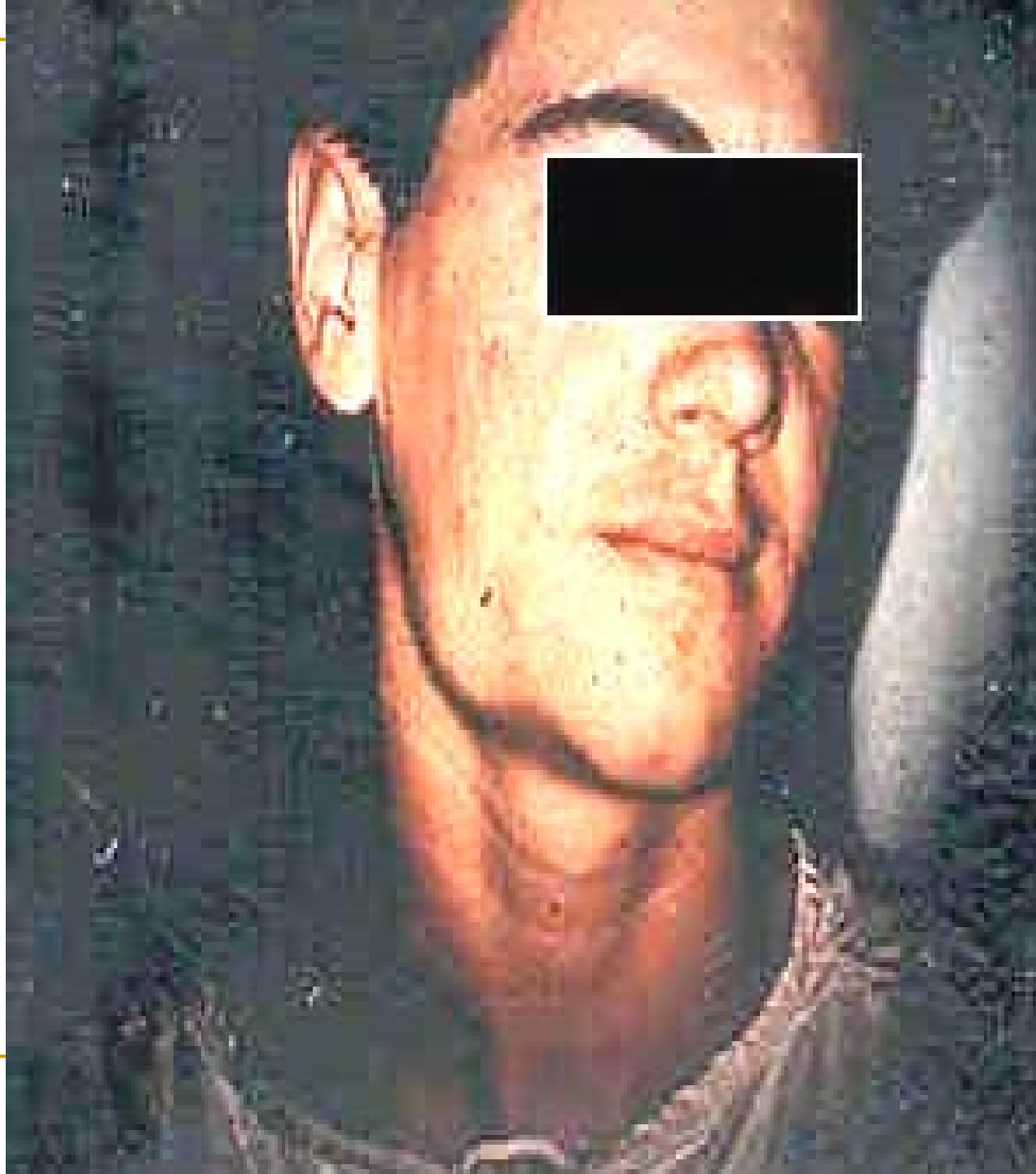
CLINICAL FEATURES

Non-Hodgkin's lymphoma

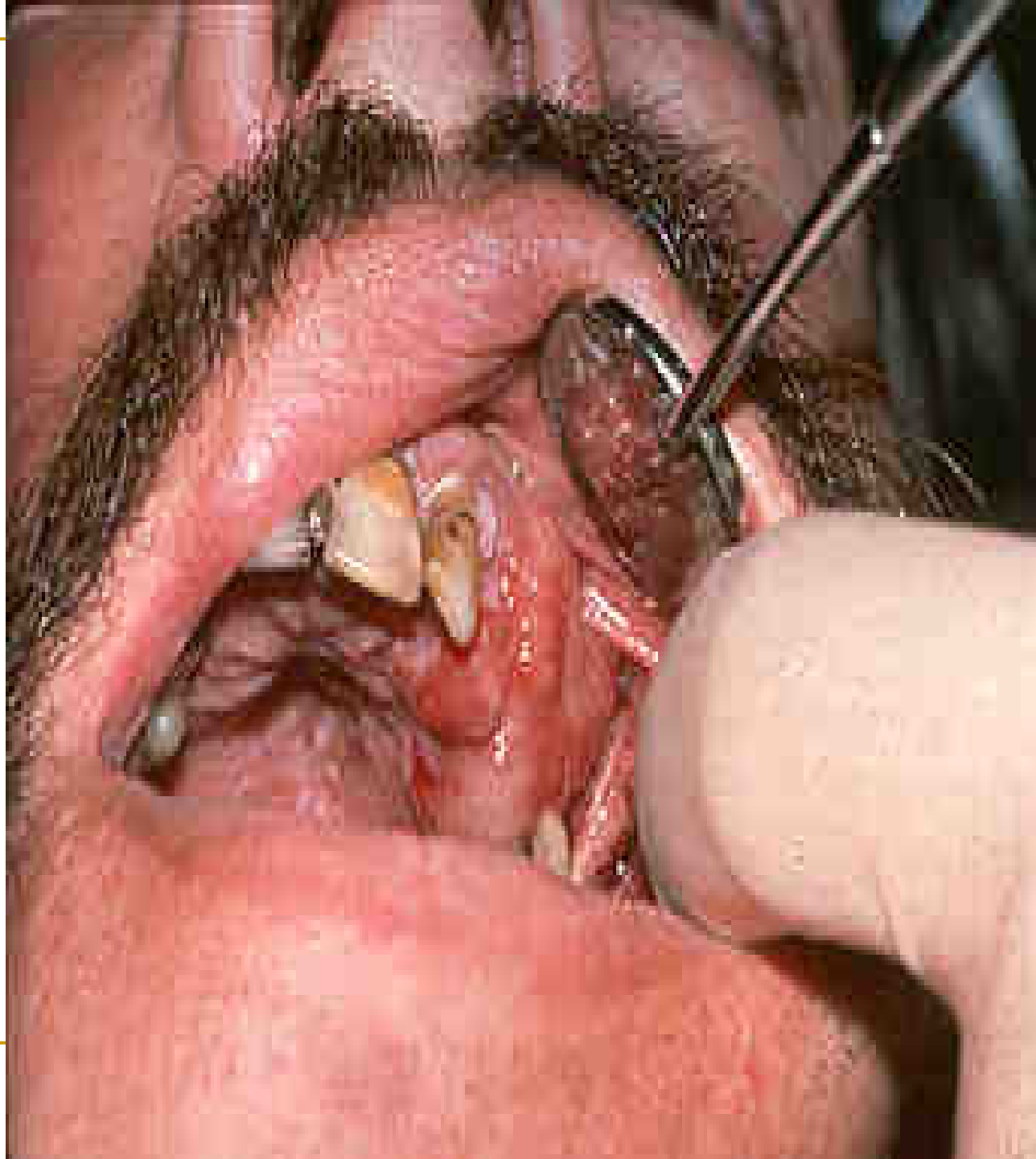
Lymphadenopathy

- Persistent, painless, peripheral adenopathy
- Centrifugal lymphadenopathy involves epitrochlear, Waldeyers Ring and abdominal nodes.
- Lymph nodes in some histopathologic subtypes of NHL frequently wax and wane.
- About 20% of patients with NHL present with mediastinal adenopathy; these patients present with cough or chest discomfort or without clinical symptoms but having an abnormal chest X-ray.
- Involvement of retroperitoneal, mesenteric and pelvic nodes is common in most histologic subtypes of NHL.

Non hodgkin’s lymphoma involving submandibular lymph node



Non hodgkin’s lymphoma eroding the buccal mucosa



CLINICAL FEATURES

Non-Hodgkin's lymphoma

- Systemic complaints, if present include weight loss, fever or night sweats. These complaints are more common in patients with diffuse aggressive histologies especially in hepatic and extranodal involvement.

- Other symptoms (although rare) include:

  Fatigue

  Malaise

  Pruritis

  Unexplained anaemia

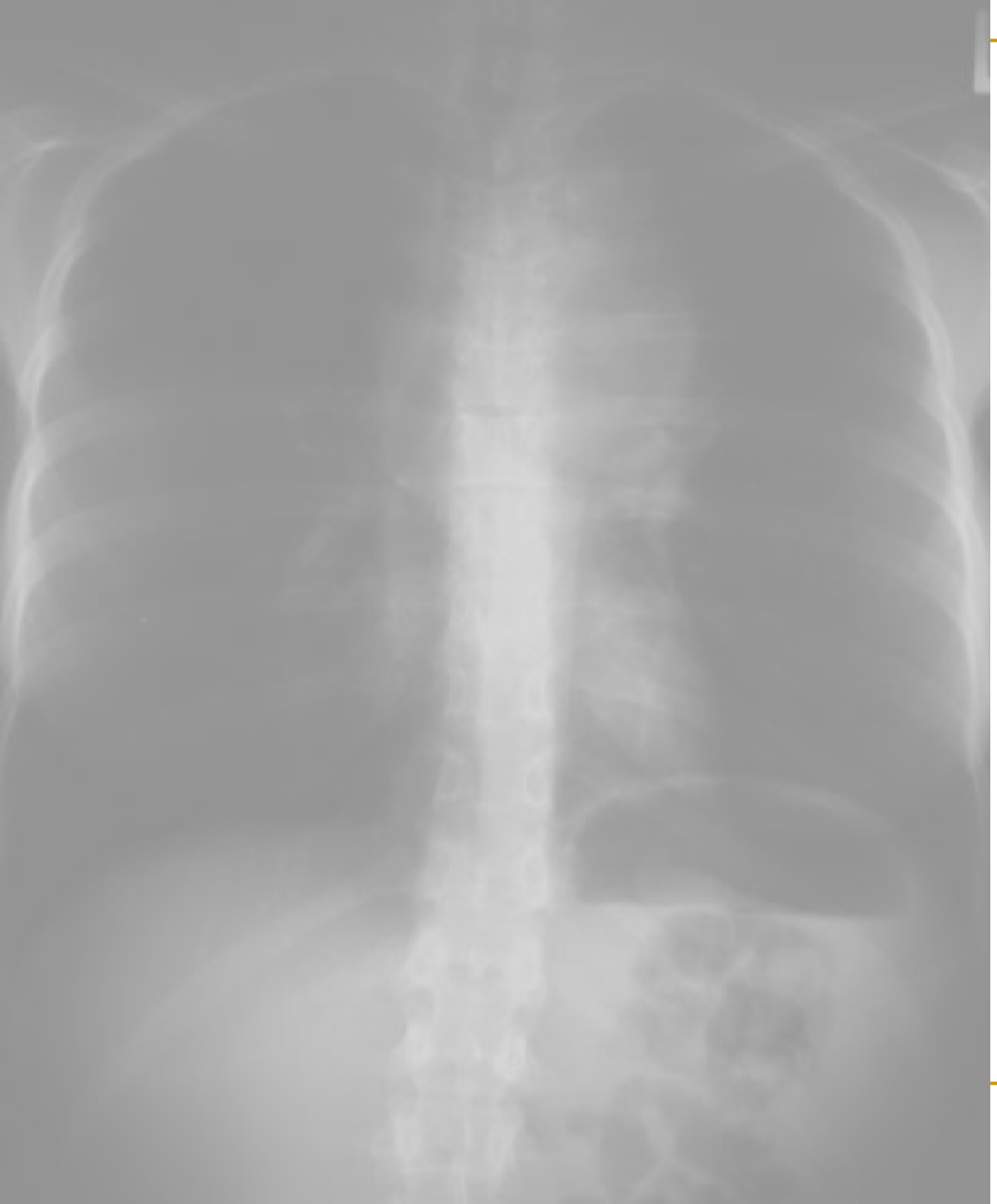
CLINICAL FEATURES

Non-Hodgkin's lymphoma

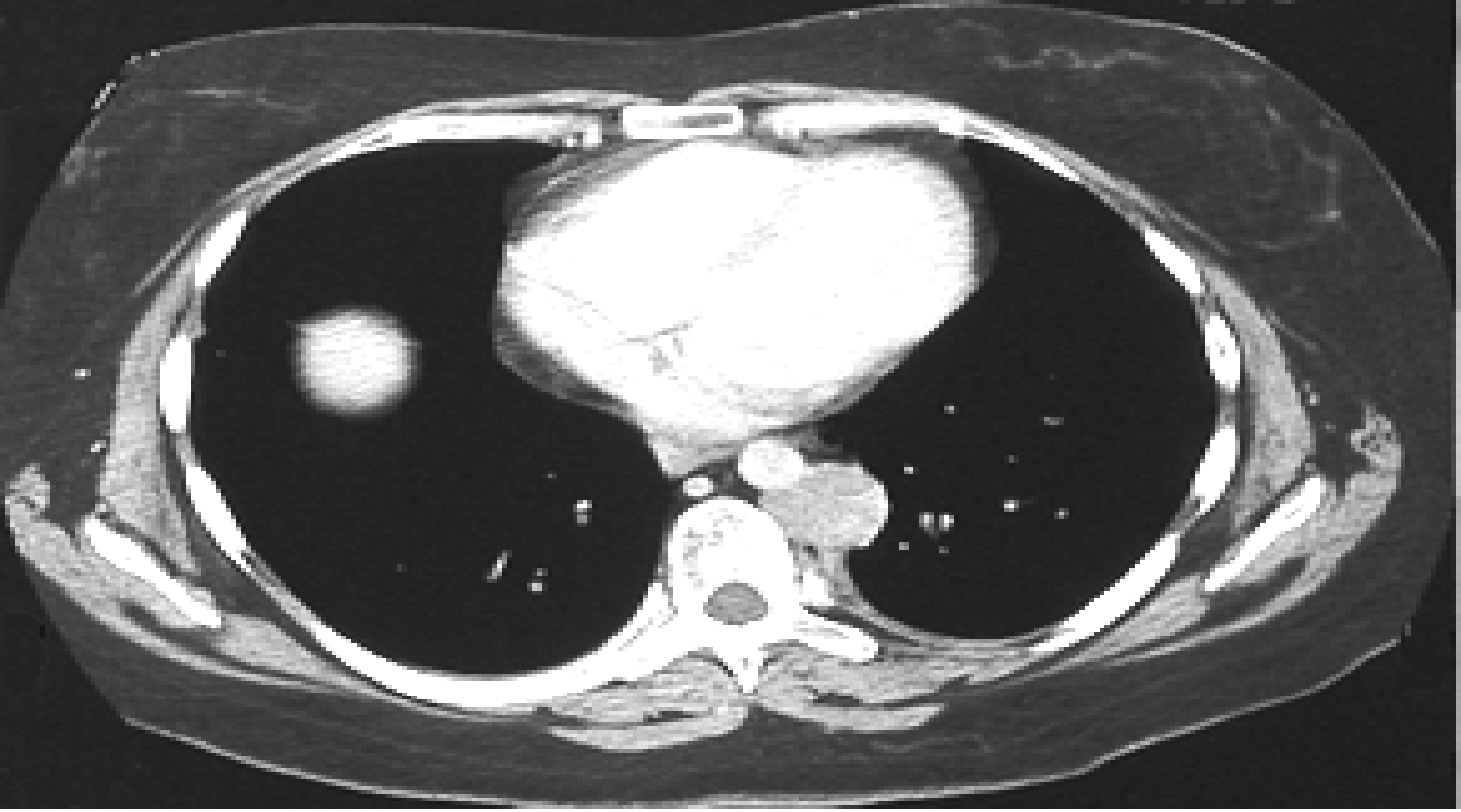
- Patients with abdominal involvement can present with :
  - chronic pain in abdomen
  - abdominal fullness
  - early satiety
  - symptoms associated with visceral obstruction
  - acute perforation and gastrointestinal haemorrhage (rare)
- Patients with aggressive NHL can present with primary cutaneous lesions, testicular masses, acute spinal cord compression, solitary bone lesions & rarely lymphomatous meningitis.

LABORATORY FINDINGS

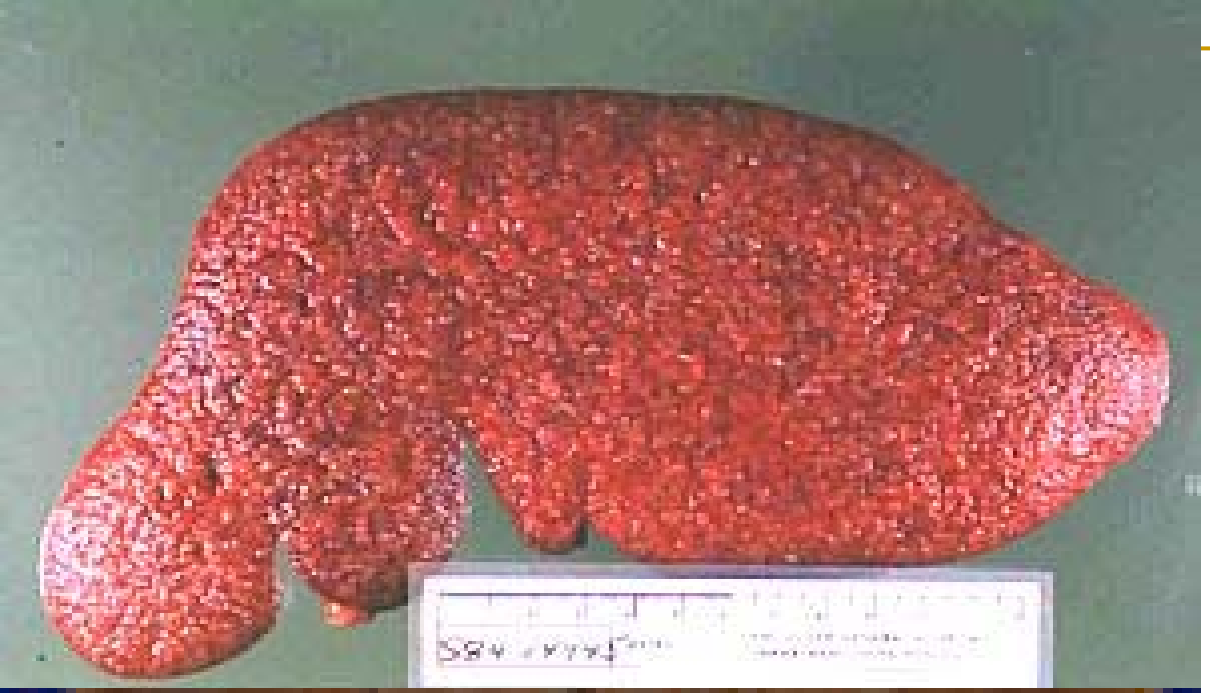
- The peripheral blood is usually normal but a number of lymphomas present in leukemic phase.
- Bone marrow involvement is manifested as para-trabecular lymphoid aggregates.
- CSF cytology may show malignant cells.
- Chest roentgenogram may show a mediastinal mass (esp. in lymphoblastic lymphoma)
- Serum LDH is a useful prognostic marker and is now incorporated in risk stratification of treatment for (NHL).

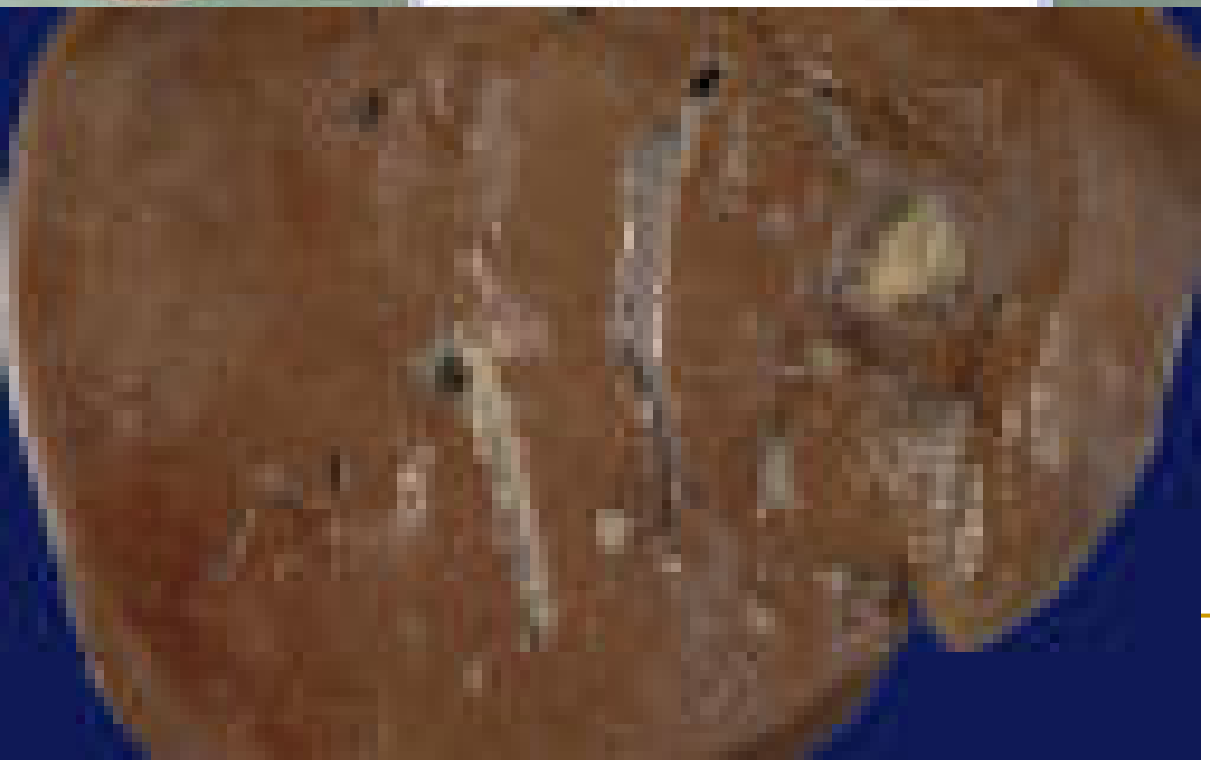


Chest X-ray P.A.view showing mediastinal lymph nodes

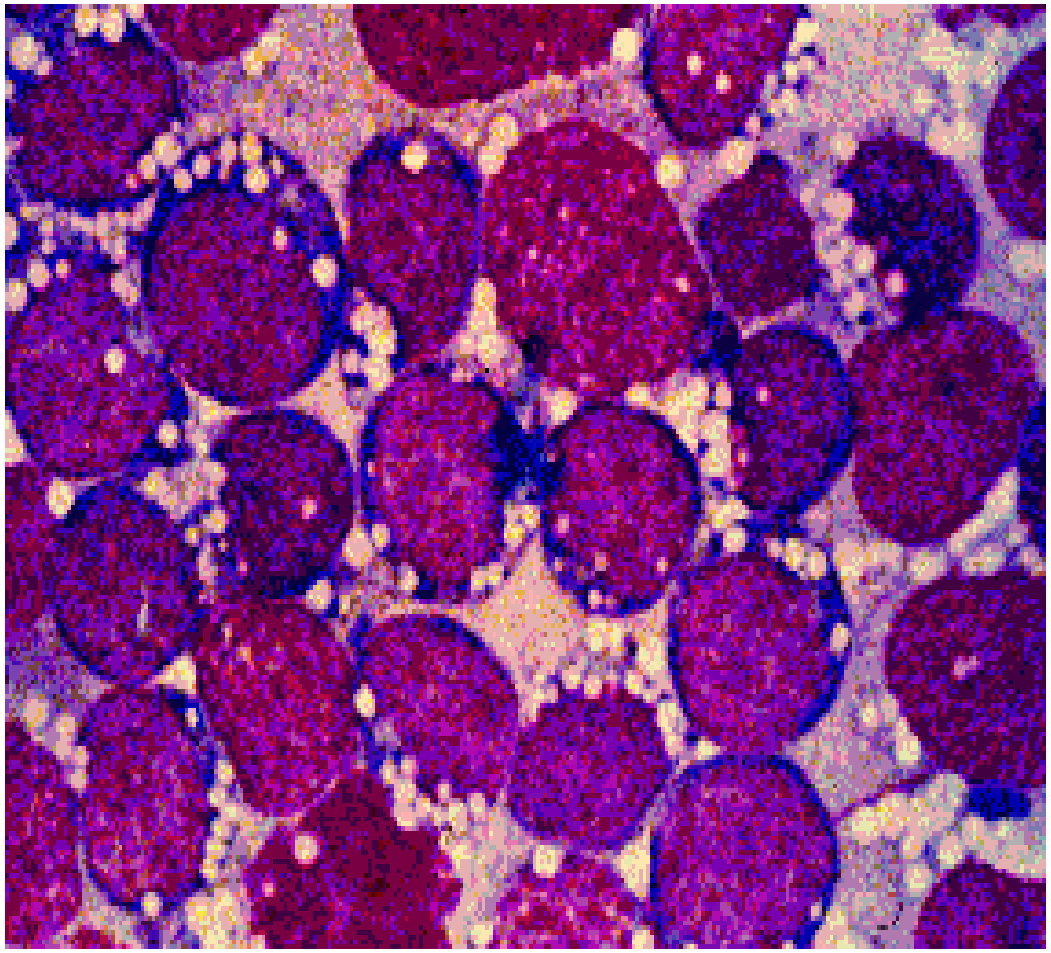


C.T. Scan revealing inolvement of para-aortic lymph node





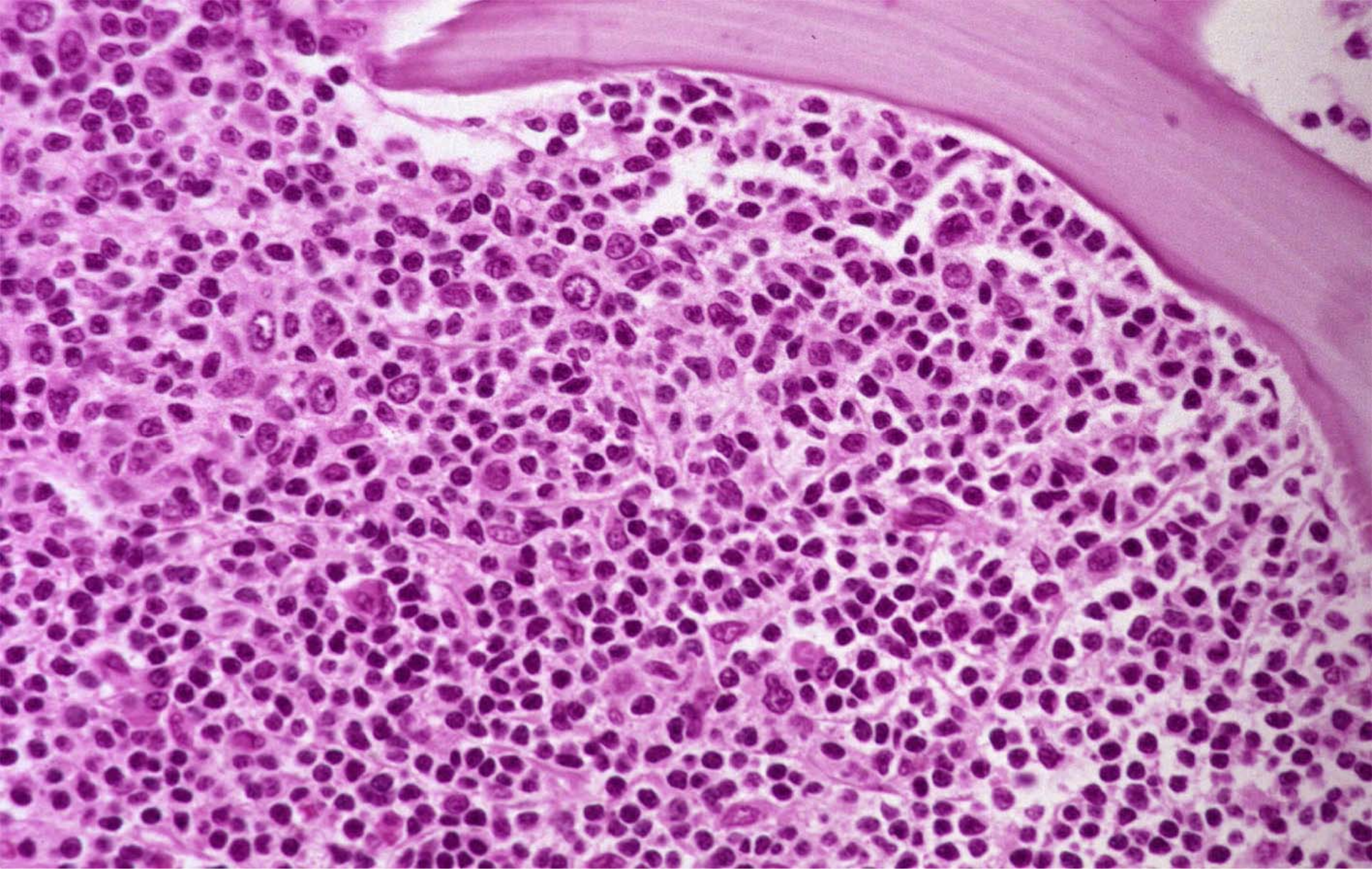
Lymphoma involving extranodal sites



Bone marrow aspirate displaying blasts with prominent cytoplasmic vacuolation s/o BURKITT'S LYMPHOMA

DIAGNOSIS

- The definitive diagnosis of lymphoma is made by tissue biopsy
- Needle aspiration may yield suspicious results but a lymph node biopsy (or biopsy of involved extranodal tissue) is required for diagnosis and staging.
- Biopsy specimen are usually from lymph nodes but may occasionally be from other tissues.



Follicular lymphoma

ANN Arbor Staging System for Lymphomas

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)

Ann Arbor Staging System for Lymphomas

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 structure in III 1

Ann Arbor Staging System for Lymphomas

IV Involvement of extranodal site 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% body weight during the 6 months before staging investigation

Unexplained, persistent, or recurrent fever with temperature 38 degree during the previous month

Recurrent drenching night sweats during the previous month

E Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow.

Staging evaluation for Hodgkin's disease

- Careful history
- Physical examination
- Complete blood count
- ESR
- Serum chemistry studies including LDH
- Chest radiograph
- CT Scan of the chest, abdomen & pelvis.
- Bone marrow biopsy
- Gallium scan (to document remission at the completion of therapy)
- Bipedal lymphaniogram

Staging evaluation for Non-Hodgkin's lymphoma

- Physical examination
- Documentation of B symptoms
- Laboratory evaluation: CBC, LFT, Uric acid, Calcium, Serum Protein electrophoresis, Serum Beta-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) in large-cell lymphoma

Treatment of Hodgkin's disease

- Patients with localized HD are cured > 90% of the times.
- Treatment involves radiation alone or the combination of radiation and chemotherapy called combined modality therapy.
- Combined modality therapy is also used for children whose growing bones and muscles cannot tolerate radiation therapy in full doses.
- In patients who fail to undergo remission or who relapse, high dose chemotherapy with stem cell transplant (bone marrow transplant) is considered.

Treatment of Hodgkin's disease

Stage	Treatment of choice
I A & II A	Brief course of chemotherapy (ABVD) + Radiotherapy to involved sites.
I B	
II B	Complete course of chemotherapy
III A & B	(ABVD) + Radiotherapy
IV A & B	

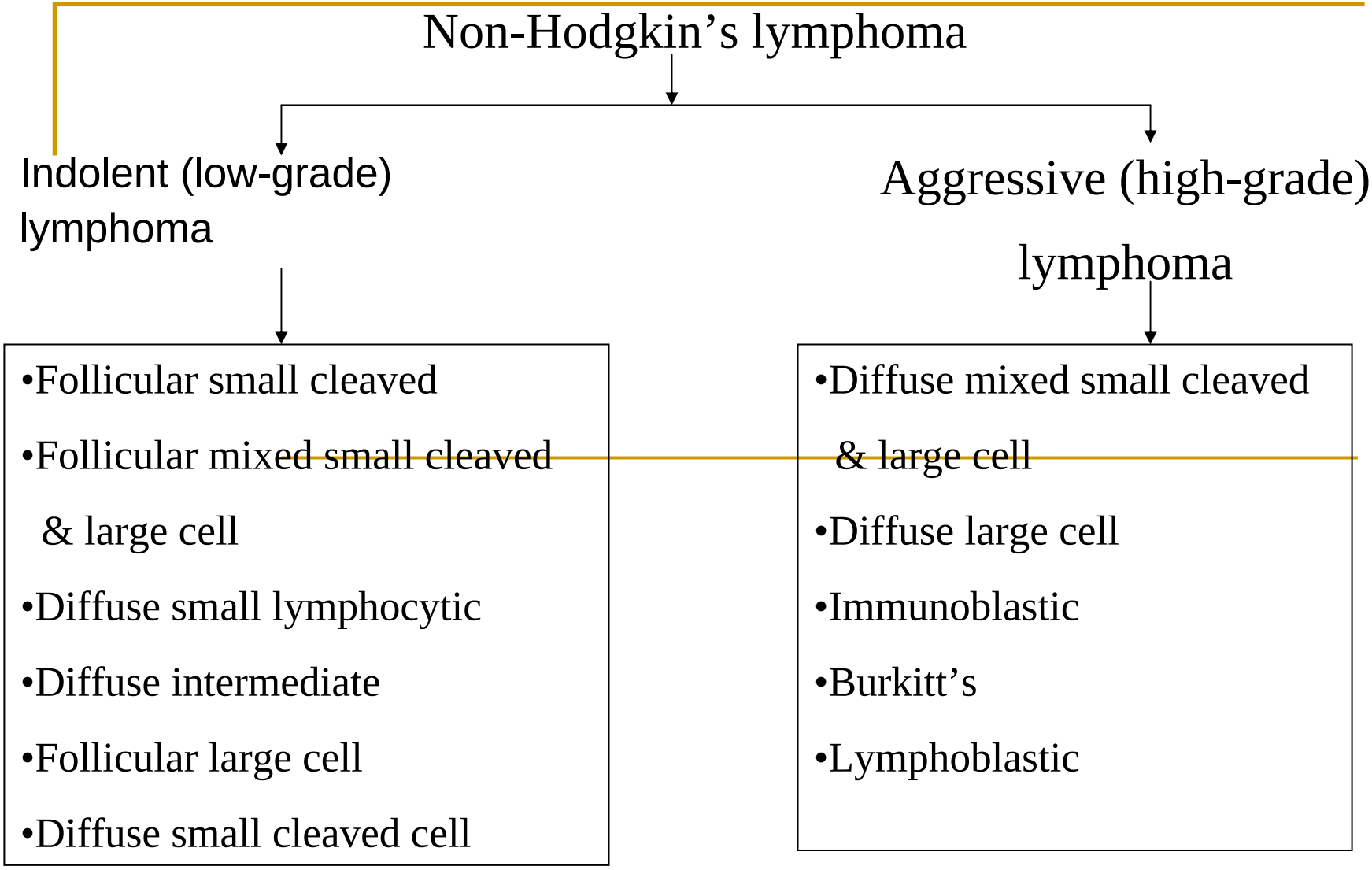
Treatment of Hodgkin's disease

- Investigational immunotherapeutic regimens also appear to have potential in preventing relapse of higher stage disease.

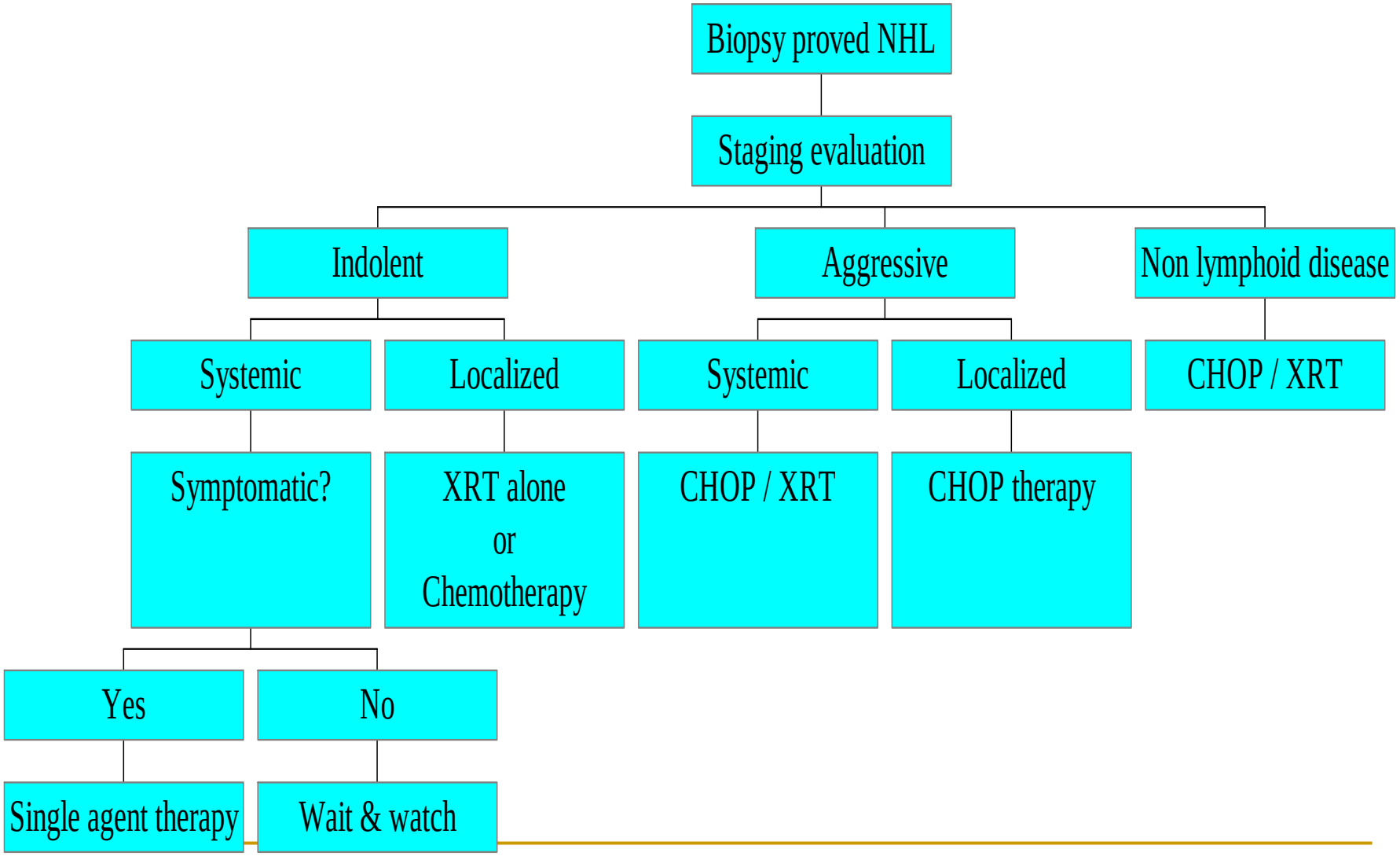
- Monoclonal antibodies to CD 30 (a surface antigen of RS cells) have been explored as vehicles for directing cytotoxins to tumor cells & preliminary results of trials using this immunotoxin appear very promising in decreasing the rate of relapse.

Cancer Treat Rev 1999; 25 : 169

Treatment of Non-Hodgkin's lymphoma



Treatment Algorithm for NHL



Curr Surg Diag Treat 2003

Treatment of Non-Hodgkin's lymphoma

- A monoclonal antibody (**Rituximab**) directed against the B cell surface antigen CD 20 is effective both as salvage therapy for relapsed low grade B cell lymphomas and as initial therapy.

- Radio-immunoconjugates that fuse anti-B cell antibodies with radiation may produce improved results with modest increases in toxicity compared with antibody alone, and one such agent (**Yttrium-90 ibritumomab tiuxetan**) is in use.*

* Blood 2003; 101: 391

Prognosis of Hodgkin's disease

- The prognosis of patients with stage I A or II A disease treated by radiotherapy is excellent with 10 - year survival rates in excess of 80%.

- Patients with disseminated disease (III B, IV) have 5 - year survival rates of 50 - 60%.

- Poor prognostic factors are:
  - Age > 60 years
  - Bulky disease
  - Lymphocyte depletion or mixed cellularity on histologic examination
  - Recurrence of disease after initial radiotherapy.

Prognosis of Non-Hodgkin's lymphoma

International Prognostic Index

- Five clinical risk factors
  - age > 60 years
  - serum LDH levels elevated
  - performance status > 2 (ECOG) or > 70 (Karnofsky)
  - Ann Arbor stage III or IV
  - > 1 site of extranodal involvement
- Patients are assigned a number for each risk factor they have
- Patients are grouped differently based upon the type of lymphoma

IPI is a powerful predictor of outcome in all subtypes of NHL.

Intern med 2000; 39: 197

Differential diagnosis of Lymphoma

1. Lymphoid hyperplasia due to infections

- Bacterial or viral pharyngitis
- Tuberculosis
- Infectious mononucleosis
- Histoplasmosis
- Toxoplasmosis
- Cat scratch disease
- CMV & EBV infections

Differential diagnosis of Lymphoma

2. Malignancy

- Naso pharyngeal cancers
- Thyroid cancers
- Breast cancer- axillary lymphadenopathy
- Tumours of the lung & mediastinum specifically small cell & non small cell carcinomas -- mediastinal lymph nodes.

3. Immune disorders such as Rheumatoid arthritis & Lupus erythematosus.

Differential diagnosis of Lymphoma

4. Castleman's disease

- presents with localized or disseminated lymphadenopathy
- disseminated form of the disease is accompanied by anemia & polyclonal hypergammaglobulinemia
- related to an overproduction of IL-6, possibly produced by human herpes virus 8.

5. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman's disease)

- presents with bulky lymphadenopathy
- seen in children or young adults
- non-progressive & self limited
- can sometimes manifest autoimmune hemolytic anemia

Differential diagnosis of Lymphoma

6. Lymphomatoid papulosis

- cutaneous lymphoproliferative disorder
- cells of lymphomatoid papulosis are similar to those seen in lymphoma & stain for CD 30
- characterized by waxing and waning skin lesions that usually heal, leaving small scars.

Approach to the patient

- Initial evaluation should include a careful history and physical examination.
- Evaluation of patients with Hodgkin's disease includes:
  - CBC
  - ESR
  - Chemistry studies reflecting major organ function
  - CT scans of the chest, abdomen & pelvis
  - Bone marrow biopsy
  - A gallium scan is not necessary for primary staging, but when it is performed at the completion of therapy it allows evaluation of persistent radiographic abnormalities, particularly the mediastinum.

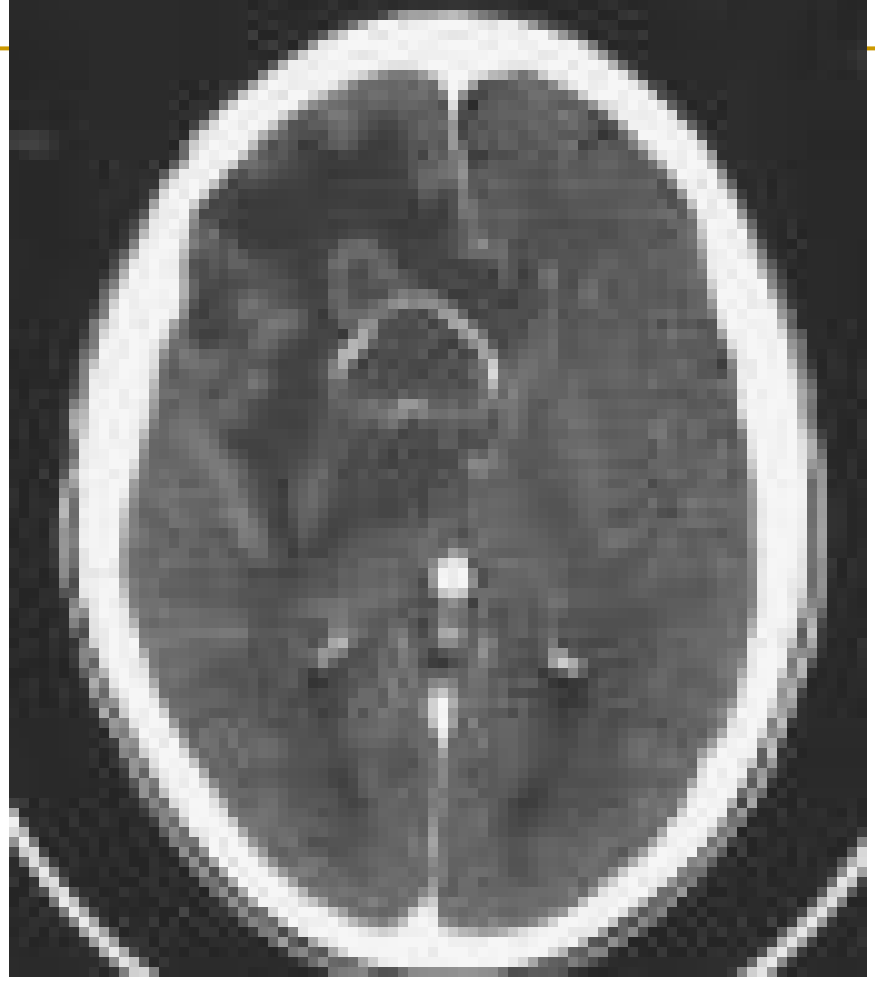
Approach to the patient

For Non-Hodgkin's lymphoma, in addition to all that is done for Hodgkin's disease, following are included in the evaluation:

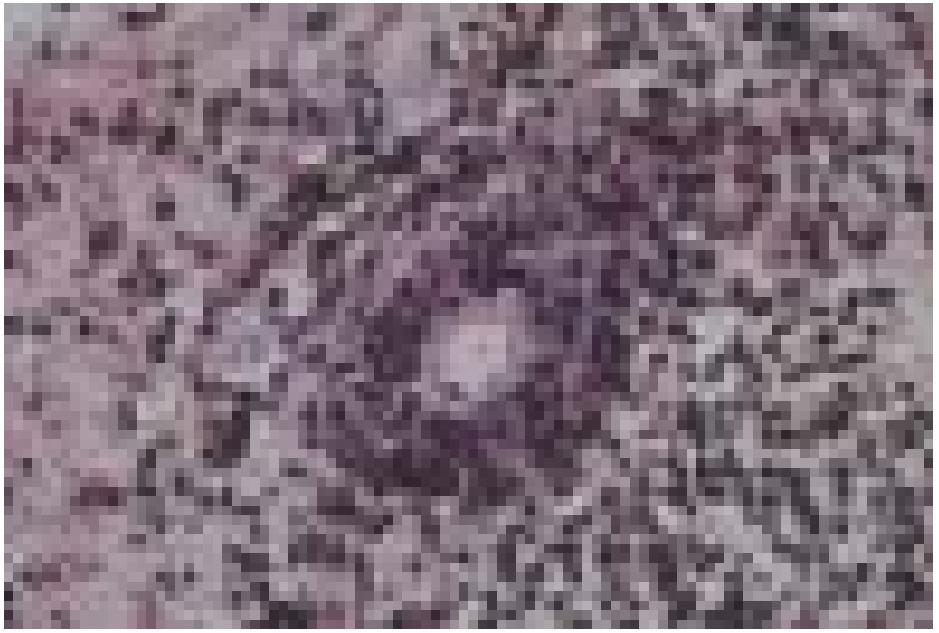
- Serum levels of LDH
- Serum Beta$_2$ microglobulin
- Serum protein electrophoresis

Lymphoma & HIV infection

- Lymphoma in HIV infected persons is almost always of Non-Hodgkin's variety.
- This lymphoma tends to be very aggressive
- Usually of B cell origin
- Characterized as diffuse large cell tumors
- Prognosis depends primarily on the degree of immunodeficiency at the time of diagnosis.
- Primary CNS lymphoma are treated with radiation



CT head revealing focal lesions with nodular ring enhancement, mass effect and surrounding edema s/o CNS lymphoma in a HIV + patient



Primary CNS lymphoma characterized by dense infiltrate of large lymphocytes with irregular nuclei.

Lymphoma & HIV infection

- Systemic disease is treated with chemotherapy, common regimens are CHOP (Cyclophosphamide, Doxorubicin, Oncovin, Prednisolone) & modified M-BACOD (Methotrexate, Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine & Dexamethasone)

- Intrathecal chemotherapy is administered to prevent or treat meningeal involvement.

All the best..