Lymphoma

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Lymphoma

- 5 th most common ca in Namibia
- Heterogeneous group of neoplasms arising from B-or T-lymphocytes in the lymphatic and reticulo-endothelial systems
- 2 main groups :
- Hodgkins lymphoma
- non-Hodgkins lymphoma
- Treatable and potentially curable

HIV – related Lymphoma

- NHL is an AIDS – defining malignancy - WHO
- Hodgins lymphoma incidence in HIV on the rise
- Early diagnosis (Stage 1 and 2) essential !! = more than 80 % curable
- Usual presentation = St. 3 and 4 and < 50 % curable

HIV-related NHL

- Most are B-cell and high grade
- In Namibia :
- DLBCL
- plasmablastic lymphoma
- Burkitt's lymphoma
- Immunoblastic , primary CNS , PEL etc.
- Multicentric Castleman disease – HHV-8

HIV –related NHL

- 60 – 90 % :
- B-symptoms : nightsweats , fever , weightloss , pruritis
- advanced stage
- extranodal disease
- co-morbid infections eg. tuberculosis
- some degree of multi-organ failure
- CD 4 count very low

HIV – related NHL

- Poor prognostic factors :
- CD 4 < 100
- ECOG PS 3 or 4
- age > 35
- stage 4
- CNS involvement
- raised LDH
- subtypes : PEL, primary CNS , BL

HIV – related NHL

- Treatment :
- HAART
- Chemotherapy + Rituximab + support + RT
- CT : R- EPOCH / R- CHOP / CHOEP
- Support with antibiotics and G-CSF
- Intrathecal chemotherapy often added
- COVID vaccination essential

HIV – related Hodgins lymphoma

- Incidence is rising significantly
- EBV –related
- 80 – 90 % present with St. 3 and 4 disease
- 80 – 90 % present with B – symptoms
- 50 – 60 % has bonemarrow involvement
- Widespread extra – nodal disease – CNS , rectum , lung
- NOT an orderly disease like in HIV negative pts

HIV – related HL

- Subtypes commonly see in HIV :
- mixed cell - classic HL
- lymphocyte depleted - classic HL
- Still treatable and potentially curable
- Rx :
- HAART + CT + RT + support
- CT : ABVD / BEACOPP / salvage DHAP

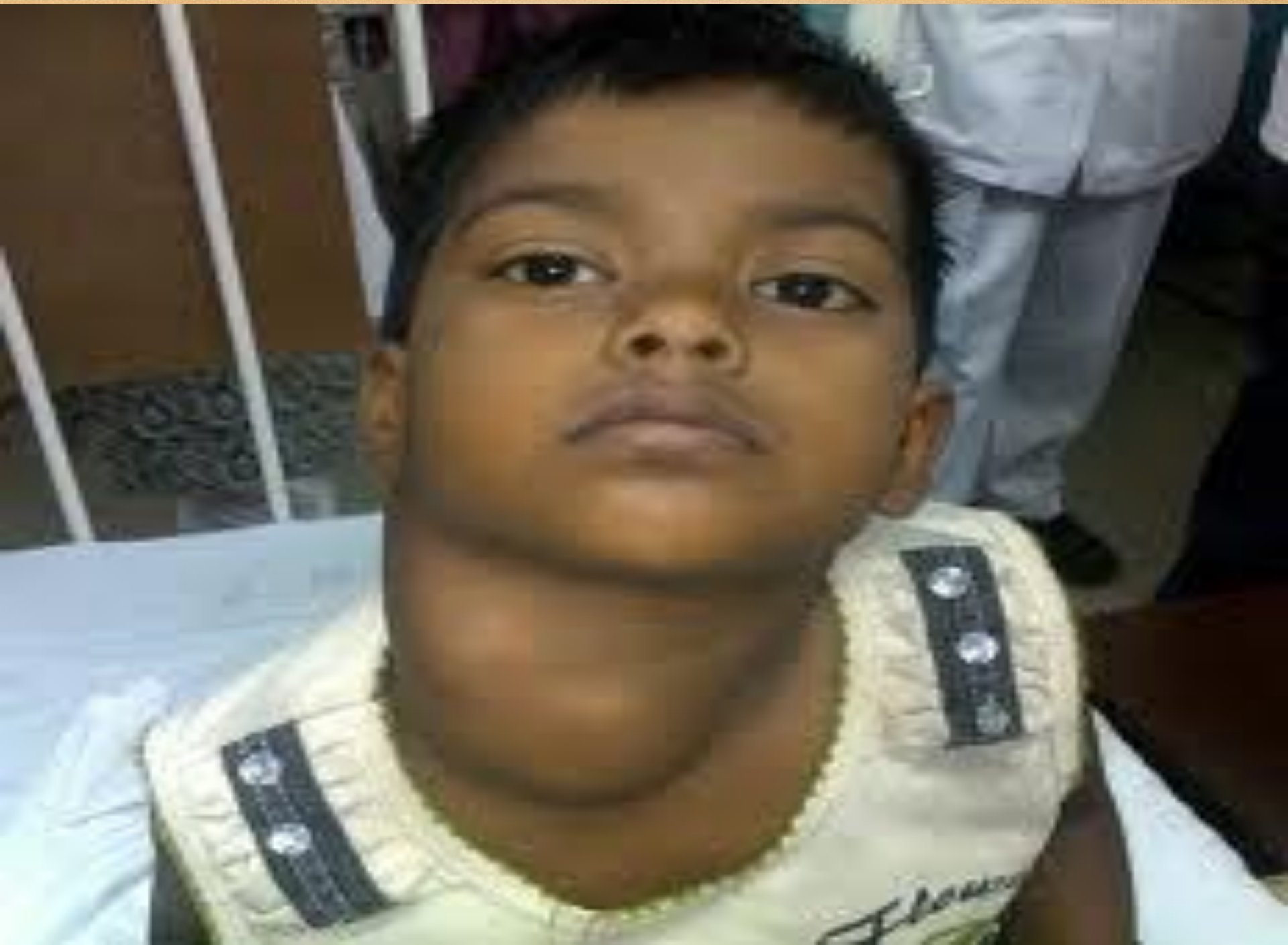
Hodgkins lymphoma = HL

- Male:female ratio 1.4 : 1
- 15 to 40 yrs
- Etiology :
- Originates from B-cells in germinal centre – Reed-Sternberg cells (giant cells with more than 1 nucleus)
- Risk factors : HIV; Epstein-Barr virus (EBV); immunosuppression eg. Post-transplant

HL

Symptoms +signs

- Painless, rubbery lymphadenopathy –often neck
- Mediastinal lymphnodes in nod.sclerosing HL
- Alcohol induced pain –in affected lymphnodes
- Hepato/splenomegaly
- B-symptoms : Pel-Ebstein fever, pruritis, nightsweats,weightloss
- Pancytopenia –low Hb,WBC, platelets (BM)



Symptoms+signs

- Bone involvement – usually osteoblastic lesions on XR's and bonescan - bonepain, fractures
- Compression symptoms :
- Sup. vena cava syndrome (med. l/n's)
- obstructive jaundice (abdominal l/n's)
- lymphoedema limbs
- paraplegia (spinal cord compression)

Symptoms + signs

- Extranodal sites rare – think of HIV if skin, bones, CNS , pleura involved or ascites
- HL : usually in specific group of l/n's; tends to spread in orderly fashion; usually does not affect abdominal l/n's; usually not extranodal; St. 1+2
- Lymphoma :
- spreads disorderly, anywhere; extranodal;St.3+4

Diagnosis

- Biopsy of entire lymphnode
- Mediastinoscopy /thoracotomy to biopsy
- Laparoscopy/laparotomy to biopsy
- Endoscopy eg. nasopharynx
- Spinal cord decompression and biopsy
- Histopathology – what type of HL ?
- Immunohistochemistry (IHC) cell surface markers) eg. CD 30 and CD 15 +

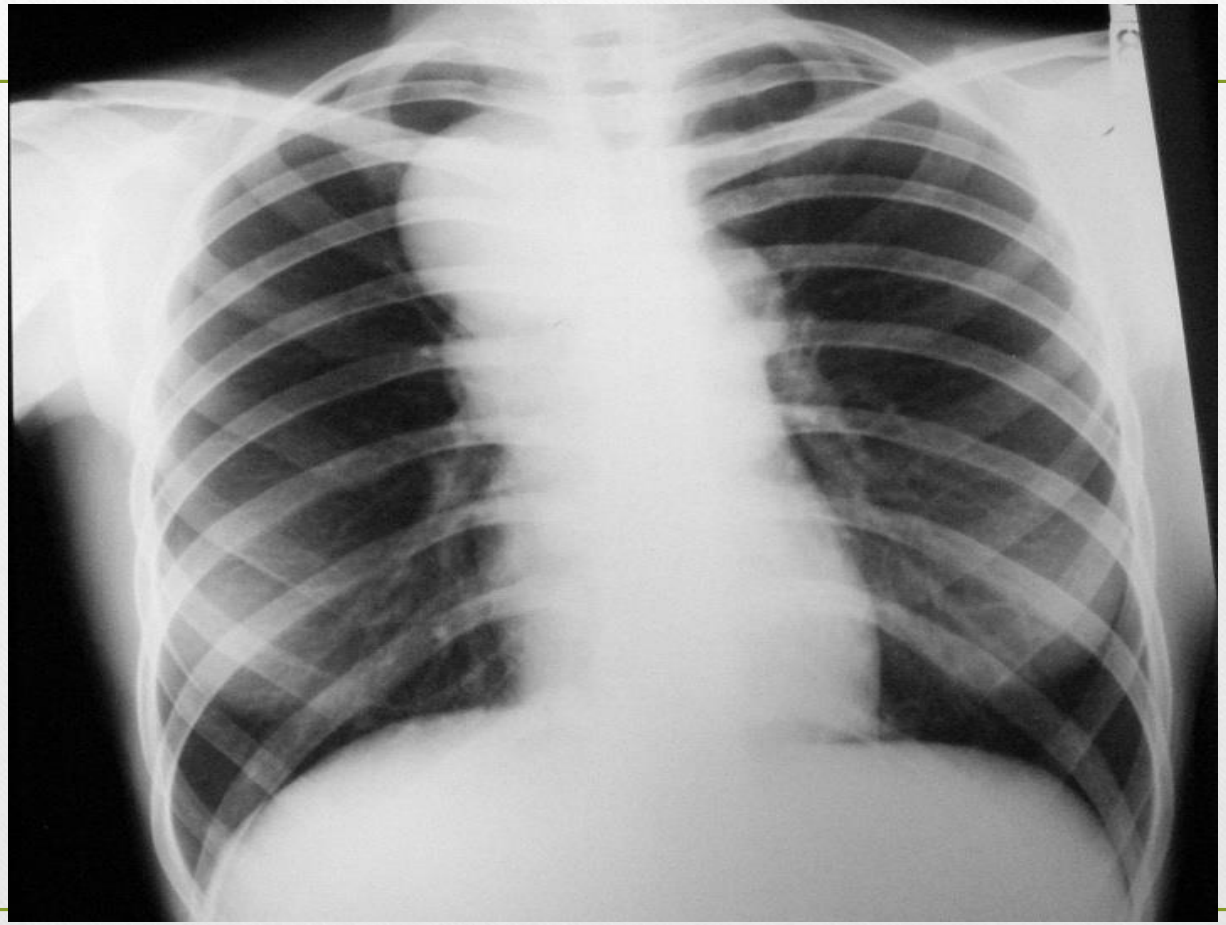
WHO classification of HL

- Classic HL : 95 % -always R-S cells; CD 15+30+
- Nodular sclerosis - 70 %
- Mixed cellularity - 25 %
- Lymphocyte rich - 3 %
- Lymphocyte depleted - rare
- Nodular lymphocytic predominant HL – 5 %
- CD 15 and CD 30 (–) CD 20 + and no R-S cells ; popcorn cells +

Staging

- History –HIV; co-morbid diseases; B-symptoms
- Physical examination incl. Performance status
- FBC, ESR, U+E, LFT, CRP, Ca, uric acid , B2 microglobulin
- CXR, CT scan thorax and abdomen ,pelvis
- Bonemarrow biopsy
- LP or brainscan if indicated
- PET/CT scan

HL



Cotswold modification of Ann Arbor

- St. 1 : in 1 lymph region only
- St. 2 : in 2 or more lymph regions on same side of diaphragm
- St. 3 : in lymph regions on both sides of the diaphragm + spleen
- St. 4 : lymphnodes + extranodal sites eg bonemarrow, liver, lung

Cotswold classification

- +A if no B- symptoms
- +B if B-symptoms (fever, nightsweats, pruritis)
  +E if extranodal involvement adjacent to l/n eg. Mediastinal l/n's + lung infiltration = St. 1E
- +X if bulky disease = l/n > 10 cm

Treatment

- Cure rate can be 75 % ; not in HIV patients
- St. 1A - RT alone
- St. 1B to St. 4 – chemotherapy x 4 – 6 cycles + RT
- Chemotherapy – ABVD or BEACOPP regime
- Radiotherapy – involved field RT
- Relapse : salvage CT + autologous stem cell transplant

Treatment

- Supportive treatment during CT and RT
- Allopurinol to prevent tumour lysis syndrome
- Antibiotics and antifungals
- Fe and folic acid
- diet
- Anti nausea (5HT 3 – antagonists) drugs
- Analgesics

Follow up

- To detect relapse early
- To diagnose late complications of treatment
- (in the 75 % who might be cured)
- hypothyroidism (RT neck)
- sterility (pelvic RT + CT)
- coronary artery disease (mediastinal RT)
- cardiomyopathy (Doxorubicin CT)

Follow up

- Lung fibrosis (Bleomycin , RT)
- Avascular necrosis of femur head (Prednisone)
- Depressed cellular immunity – TB , CMV, Pneumocystis carinii, Herpes zoster
- Second malignancies eg. AML, NHL, breast cancer, lung cancer, melanoma, sarcoma - usually 7-10 years later or more

Follow up

- Every 3 months for 2 years
- 6 monthly from 2 to 5 years
- Annually after 5 years
- History; clinical examination; FBC, ESR, LFT, CRP, B2 microglobulin, CXR, thyroid functions, CT scans if indicated

Non-Hodgkins lymphoma =NHL

- Heterogeneous group of neoplasms involving malignant monoclonal proliferation of lymphoid cells in lymphnodes, bonemarrow, spleen , liver and GI tract
- More common than HL
- >80 % arise in B-cells
- < 20% arise in T-cells or NK cells (natural killer)

NHL

- Most common lymphomas in children and teenagers are Burkitt's lymphoma and lymphoblastic lymphoma
- Most common lymphoma in all ages (adults) – DLBCL = diffuse large B-cell lymphoma
- Most common lymphoma in middle age and old age – follicular lymphoma

Etiology

- Viruses :
- RNA : HIV (+ co-virus)
- HTLV1 = human T-cell lymphotropic virus type 1 - adult T-cell leukaemia – lymphoma
- DNA : EBV – Burkitt's and DLBCL etc.
- HHV-8 - MCD , PEL
- Viral DNA is inserted into the host genome and disrupts normal growth control

Etiology

- EBV infects many people without causing illness; it infects the B- lymphocytes and nasopharynx epithelium. When EBV infected cells are exposed to other stimuli eg. Malaria, malignancy can occur (activation of c-myc oncogene)
- EBV can cause Burkitt's and other lymphomas and nasopharynx cancer and gastric cancer

Etiology

- H. Pylori (Helicobacter pylori) infection of gastric mucosa can cause MALT – lymphoma
- (mucosa-associated lymphoid tissue)
- H. Pylori can also cause gastric cancer
- Immunodeficiency causes lymphoma
- HIV
- post organ transplant
- congenital immunodeficiency syndromes

Etiology

- Auto-immune disorders eg. SLE, RA, Sjogren's
- Phenytoin
- Previous chemotherapy/ radiotherapy

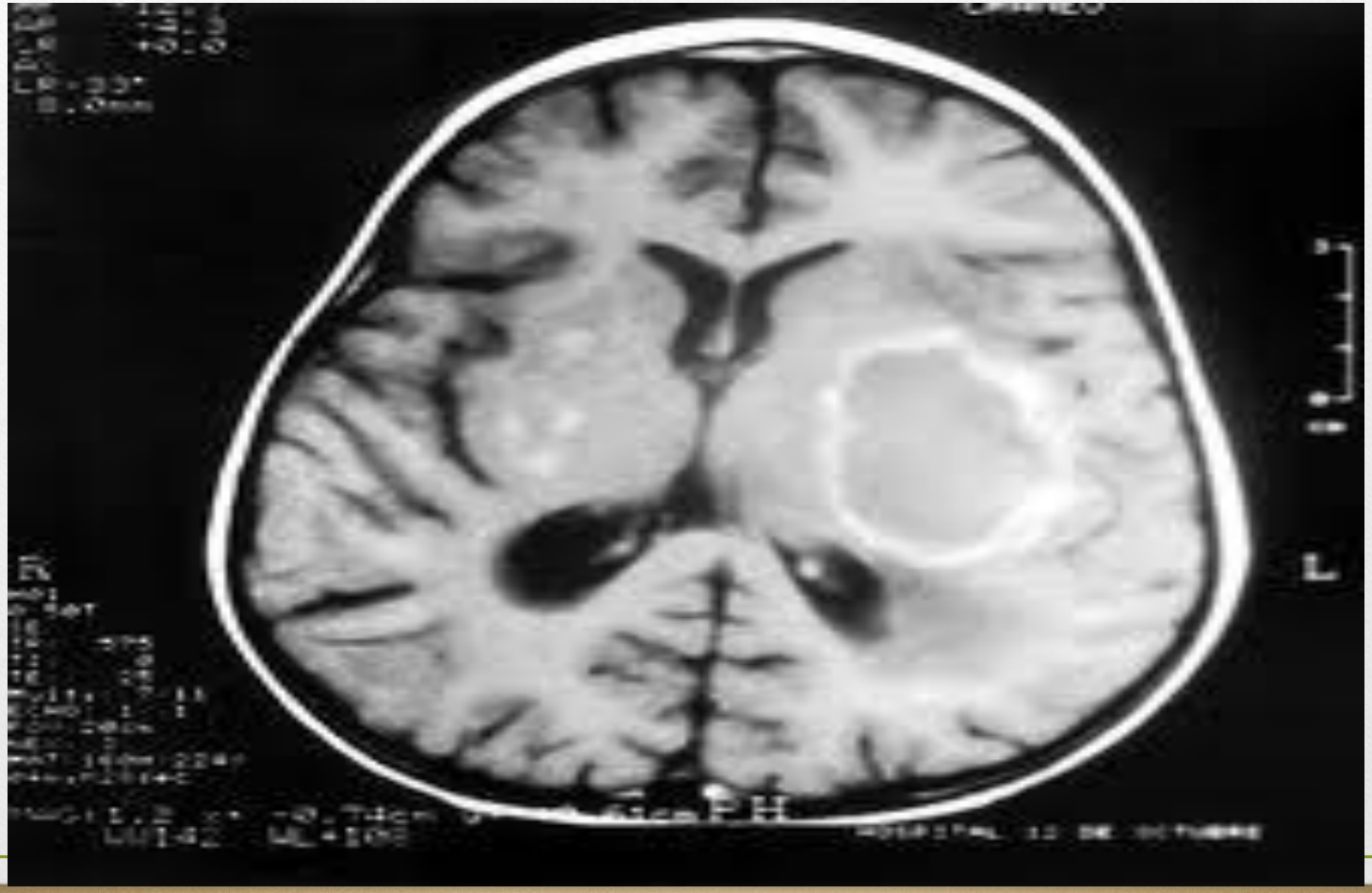
Symptoms + signs

- Painless, rubbery hard lymphadenopathy – later matted
- Hepatosplenomegaly
- Pancytopenia
- Extranodal involvement – skin, stomach, GIT, CNS, lungs, bones – causing ulcers, obstruction, bleeding, convulsions, pleural effusions, paraplegia, pain, ascites, renal failure

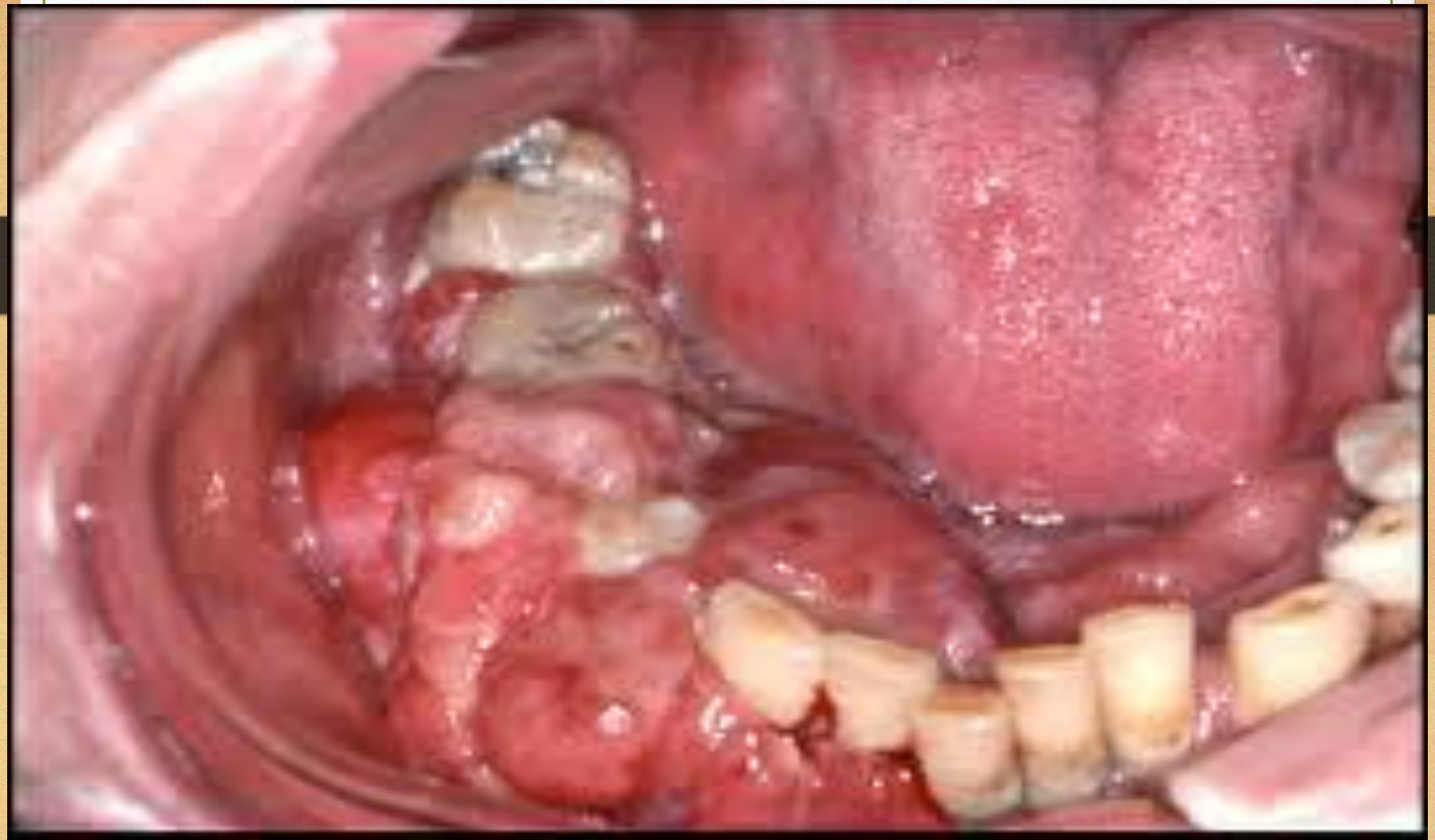
Symptoms+ signs

- B-symptoms :
- fever, nightsweats, pruritis, weightloss
- Burkitt's common in jaw or facial bones eg maxilla in endemic (African) type
- Burkitt's in sporadic (non- African) type common in breasts, ovaries, kidneys, abdomen
- Mycosis fungoides = T-cell skin lymphoma; causes nodular, ulcerating skin lesions

NHL brain



NHL



Differential Diagnosis

- Neck :
- TB
- metastatic ca from oral cavity, nasopharynx, lung, stomach, oesophagus, prostate, larynx, cervix, thyroid
- infectious mononucleosis
- oral infections eg. Dental abscess

DD

- Mediastinal lymphnodes :
- TB
- sarcoidosis
- thymoma
- mediastinal goitre
- germ cell tumours eg. Seminoma, teratoma

DD

- Axillary lymphnode :
- TB
- breast cancer
- abscess
- metastatic ca
- Abdominal / pelvic lymphnode :
- TB
- metastatic ca

Diagnosis

- Lymphnode biopsy :
- FNAB to determine lymphoma or carcinoma
- if lymphoma ; do excisional biopsy – endoscopy, laparotomy, thoracotomy etc.
- if ca ; look for primary cancer
- Bx : do histopathlogy and IHC
- B-cell = CD 20 + or T- cell = CD 3 +
- CD 20 + ? Can add anti-CD 20 MAB Rx

WHO classification of NHL

- B- cell origin : CD 10, 19, 20 +
- Indolent lymphoma : (low grade)
- Follicular lymphoma – CD 20 +, common
- CLL/SLL = chronic lymphocytic leukaemia / small lymphocytic lymphoma - lymphocytosis
- marginal zone lymphoma eg. MALT lymphoma – often in stomach ; splenic MZL ; nodal MZL

WHO classification

- B-cell :
- Aggressive lymphoma : (intermediate grade)
- DLBCL – most common type - CD 20 +,
- extranodal sites common
- mantle cell lymphoma – often affects GIT and bonemarrow ; poor prognosis

WHO classification

- B- cell :
- Highly aggressive (high grade) lymphoma :
- Burkitt's – c-myc oncogene, t(8,14) translocation
- lymphoblastic lymphoma (closely related to acute lymphoblastic leukaemia)
- HIV –related B- cell lymphomas

WHO classification

- T-cell and NK cell origin : CD 2, 3, 4 +
- peripheral T-cell lymphoma
- Mucosis fungoides / Sezary syndrome – skin
- aggressive NK cell leukaemia = fatal

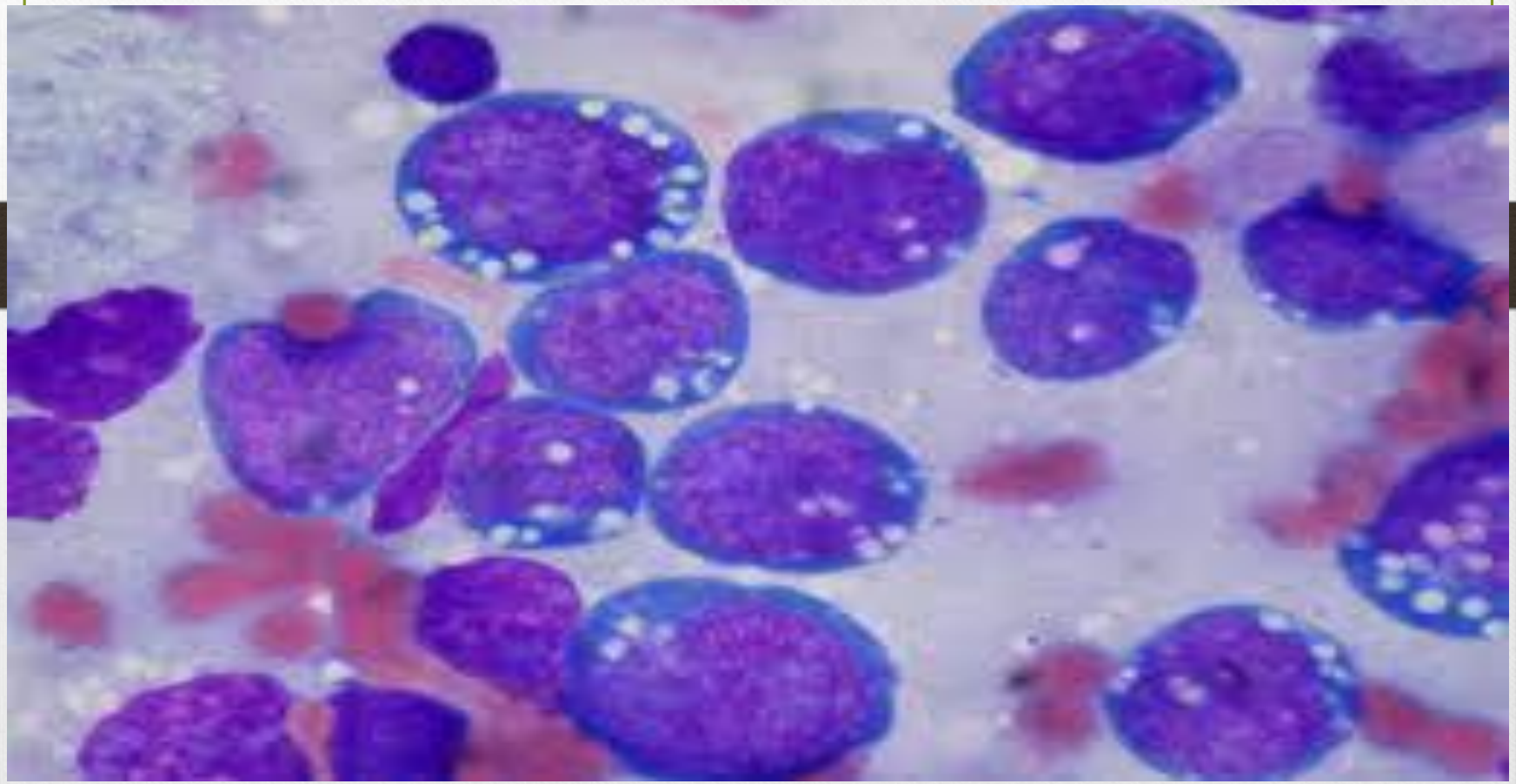
NHL

- HIV – related B-cell lymphomas :
- DLBCL (EBV)
- Burkitt's lymphoma (EBV)
- plasmablastic lymphoma (EBV or HHV 8)
- primary CNS lymphoma (EBV)
- primary effusion lymphoma (HHV8)
- NHL ass. with Castleman's disease (HHV8)

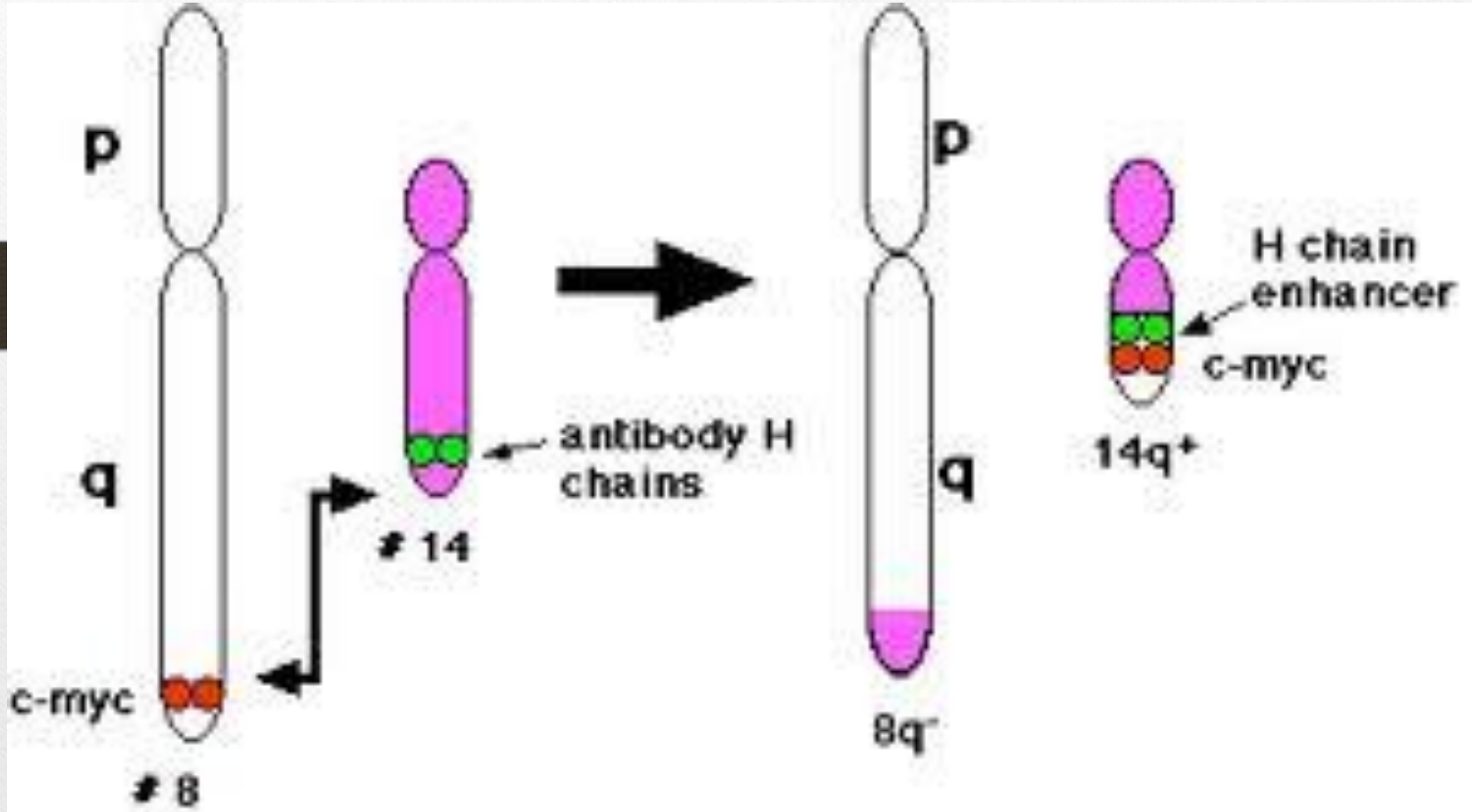
Burkitt's lymphoma

- Typical " starry sky " appearance on histology
- Endemic (African) type
- EBV +
- t (8,14) translocation
- sites – often jaw or orbit
- mostly in children and young adults
- needs chemotherapy and CNS Rx

Burkitt's



Burkitt's



Burkitt's

Burkitt's lymphoma

- Sporadic (non- African) type :
- EBV negative
- t(8,14) translocation
- affects abdomen, bonemarrow, breasts, ovaries, liver, spleen, CNS
- needs very aggressive chemotherapy
- poor prognosis

DLBCL

- GCB (germinal centre B-cell) type
- ABC (activated B-cell) type – poor prognosis use gene expression profiling to distinguish
- Always do c-myc and BCL 2 and 6 - if double or triple hit mutations - very poor prognosis and Rx should be more aggressive
- ? Rx like Burkitt's or add Velcade (Bortezumib)

DLBCL variants

- Primary mediastinal B-cell lymphoma
- Anaplastic large B-cell lymphoma
- Burkitt's – like DLBCL
- Immunoblastic lymphoma
- Centroblastic lymphoma
- B-cell lymphoma rich in T-cells
- B-cell lymphoma rich in histiocytes

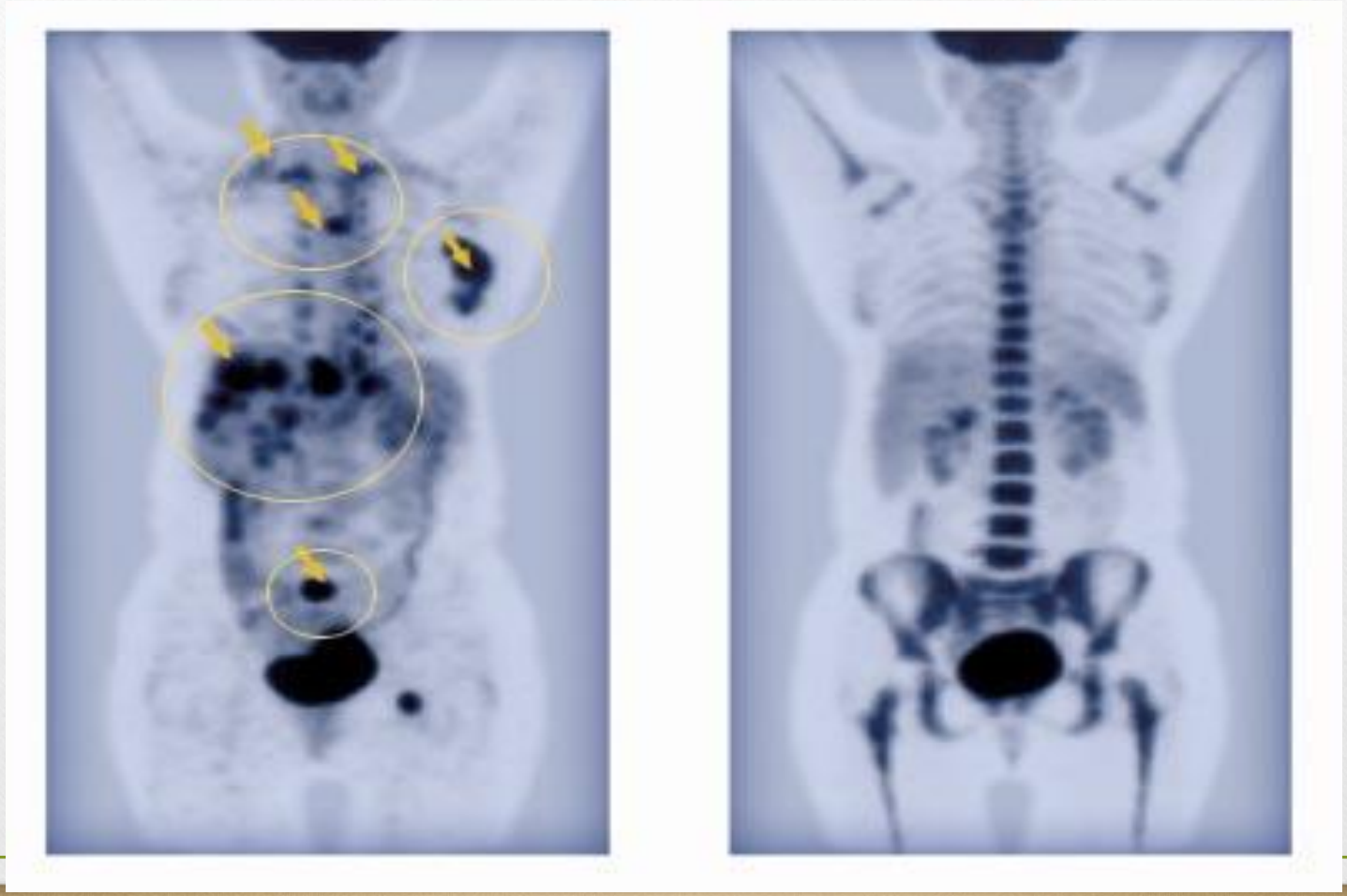
Staging

- History : symptoms, B- symptoms, co-morbid diseases, treatment eg. ARV's
- Clinical examination
- FBC, ESR, LFT, Ca, Immunoglobulins, CRP, HIV + CD4 count, U+e , B2 microglobulin
- Bonemarrow biopsy, flowcytometry, cytogenetics eg. t(8,14) in Burkitt's, t (14,18) in follicular lymphoma t (11,14) in MCL

Staging

- CXR, CT scans of chest, abdomen, pelvis, LP
- Endoscopies if indicated eg. Colonoscopy if rectal bleeding
- PET/CT scan

NHL – PET scan



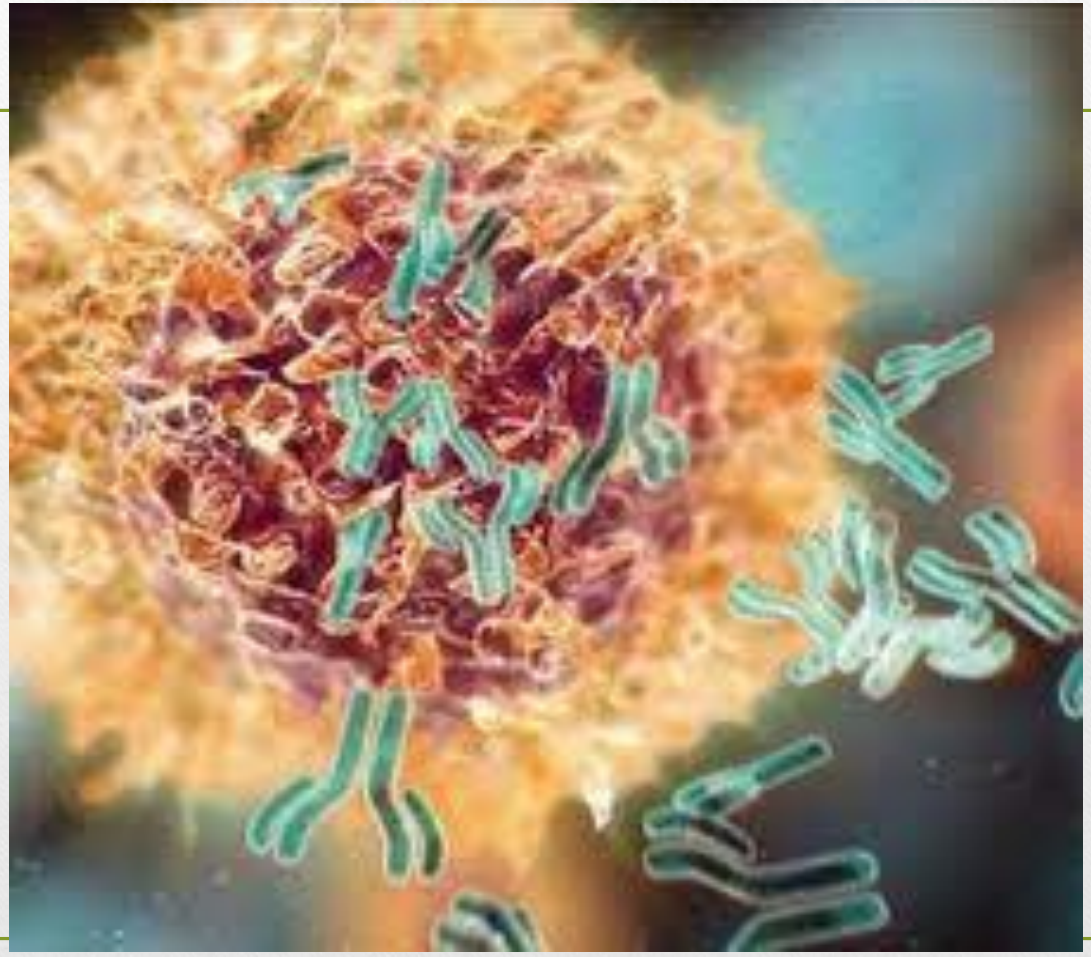
Staging systems

- Cotswold modification of Ann Arbor staging
- IPI score / FLIPI in foll. lymphoma
- age > 60
- raised LDH
- poor performance status
- Stage 3 or 4
- > 1 extranodal site
- Rai / Binet score in CLL/SLL

Treatment

- Indolent lymphomas :
- watch and wait in CLL/SLL
- less aggressive chemotherapy eg. oral Chlorambucil, COP regimes
- RT
- Rituximab = anti-CD 20 monoclonal antibody
- =biologic response modifier

NHL - Rituximab

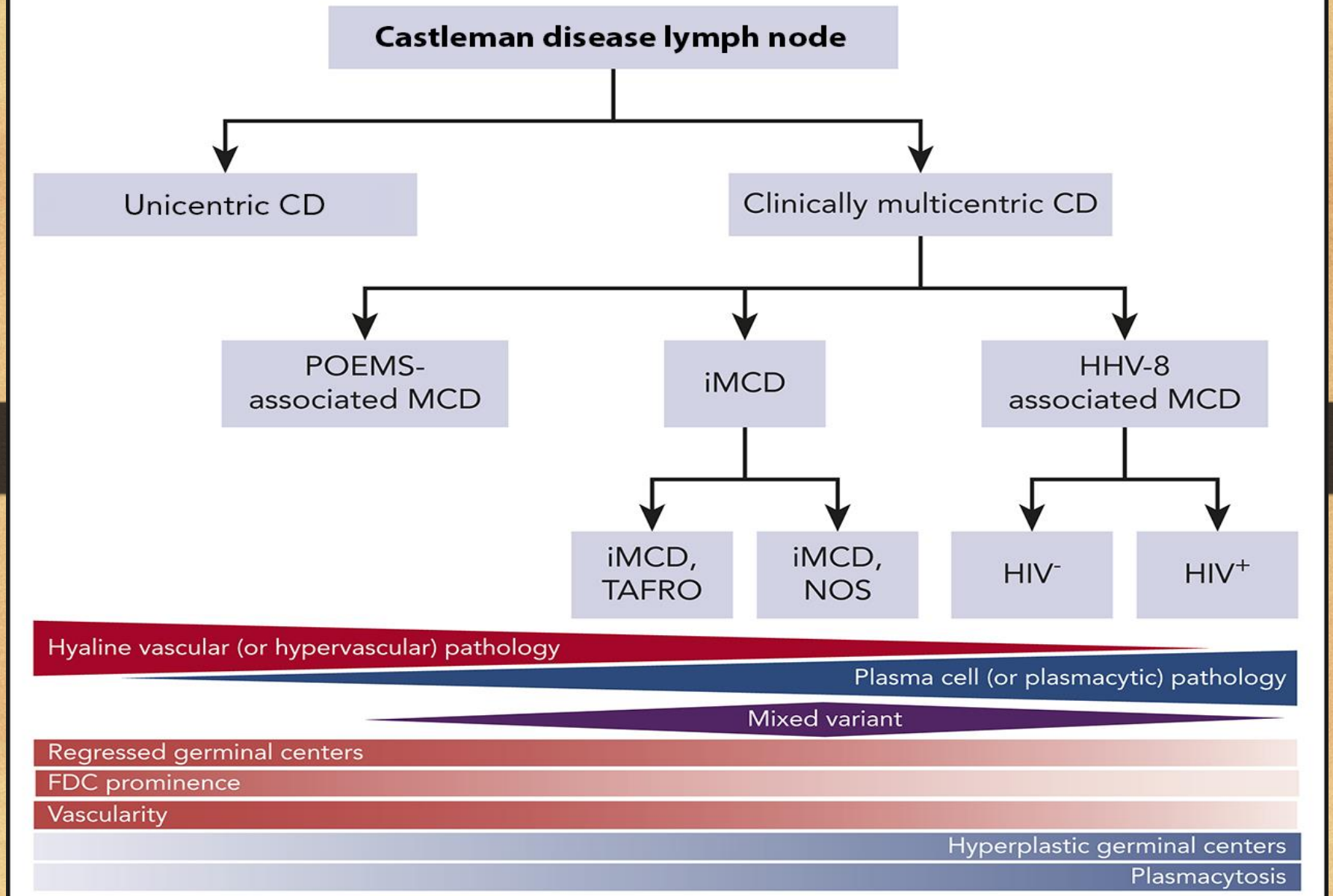


Treatment

- High grade lymphomas :
- Aggressive chemotherapy + Rituximab if CD 20 + eg. R-CHOP + CNS prophylaxis
- relapse – salvage chemotherapy and stem cell transplant
- SCT – autologous (own stemcells)
- - allogeneic (sibling or matched unrelated donor)

Multicentric Castleman disease

- Heterogeneous cluster of disorders , characterized by lymphadenopathy with unique histological features and associated with cytokine – driven (IL-6) constitutional symptoms and biochemical disturbances.
- Some caused by HHV-8 , mostly in HIV patients = a malignancy ; some driven by IL-6 causing auto-immune syndromes eg. TAFRO / POEMS


Castleman disease lymph node
Unicentric CD
Clinically multicentric CD
POEMS-associated MCD
iMCD
HHV-8 associated MCD
iMCD, TAFRO
iMCD, NOS
HIV-
HIV+
Hyaline vascular (or hypervascular) pathology
Plasma cell (or plasmacytic) pathology
Mixed variant
Regressed germinal centers
FDC prominence
Vascularity
Hyperplastic germinal centers
Plasmacytosis

MCD

- The HIV / HHV-8 subtype very common in Namibia ; cannot be distinguished from lymphoma without histology

- HHV-8 infects B-lymphocytes (MCD / PEL)
- Macrophages / dendritic cells
- Endothelial cells (KS)

MCD

- vIL – 6 is produced in germinal centres of involved lymphnodes causing B- symptoms , severe inflammatory vascular leak syndrome with ascites , pleural effusions , pericardial effusion and oedema ; as well as auto-immune syndromes such as ITP, HA , POEMS , TAFRO

MCD

- Clinical presentation :
- Lymphadenopathy , hepatosplenomegaly + B-symptoms + ITP or HA and other hyper-immune syndromes
- Histology :
- Hyaline vascular variant
- Plasmacell or plasmablast variant - HIV

MCD

- Treatment :
- Rituximab weekly x 4
- R + Etoposide / CHOEP / liposomal Dox
- ?? Valganciclovir + Zidovudine
- anti – IL – 6 Rx eg. Siltuximab (MAB)
- Tocilizumab
- Siltuximab looks promising

MCD

- Prognosis :
- Good if uncomplicated – Rx is Rituximab only
- Very poor if complicated by severe auto-immune syndromes / inflammatory vascular leak syndrome / PEL / plasmablastic lymphoma or KS

Summary

- Be aware of lymphoma in HIV patients
- Early diagnosis and Rx – fairly good OS
- Proper histology , staging , Rx , follow up
- Rx often individualized ; monitor response
- Supportive Rx's : G-CSF , antibiotics , FBC weekly , HAART
- RT as indicated
- Palliative care and psychosocial support

Lymphoma

MEDICINE IS THE ART OF USING SCIENCE TO MINISTER TO YOUR PATIENTS

THANK YOU