Lymphoma

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Lymphoma

- 5th 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:
  - CD4 < 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 seen 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
Hodgkin's 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 e.g. Post-transplant
Normal lymphocyte

Reed-Sternberg Cell
Symptoms + signs

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

- Bone involvement – usually osteoblastic lesions on XR’s and bonescan - bone pain, 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, night sweats, 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 lymphotrophic 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 histopathology 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 bone marrow; 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, bone marrow, 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
- Bone marrow 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 autoimmune syndromes eg. TAFRO / POEMS
Castlemann disease lymph node

Unicentric CD

POEMS-associated MCD

iMCD

iMCD, TAFRO

iMCD, NOS

Clinically multicentric CD

HHV-8 associated MCD

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