Approaches in Hematology

Hematology Made Easy

Non-Hodgkin's Lymphoma

✓ **Non-Hodgkin Lymphoma** is a malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells.

✓ **Classification:** it can originate from both B- (85%) and T- or NK- (15%) cells

- B-cell NHL: e.g., diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, and mantle cell lymphoma. WHO/REAL classification system are 3 categories of NHLs based on natural history:
  1. Indolent (35-40% of NHL): e.g., Follicular lymphoma, small lymphocytic lymphoma/CLL, and mantle cell lymphoma
  2. Aggressive (~50% of NHL): e.g., Diffuse large B-cell lymphoma.
  3. Highly aggressive (~5% of NHL): e.g., Burkitt's lymphoma

- T-cell NHL: e.g., mycosis fungoides (indolent TCL of the skin), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS), and anaplastic large cell lymphoma.

✓ **Clinical Features**

- Painless superficial lymphadenopathy, usually >1 lymph node region, rapid growth in aggressive lymphomas.
- Can have localized or widespread adenopathy (more common in indolent NHL)
- Constitutional symptoms are not as common as in Hodgkin lymphoma.
- Cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when BM is involved.
- Abdominal signs ± hepatosplenomegaly, retroperitoneal, and mesenteric involvement
- Oropharyngeal involvement in 5-10% with a sore throat and obstructive apnea.
- Extranodal involvement: most commonly GI tract, testes, bone, and kidney.
- CNS involvement in 1% (often with HIV, Testicular diffuse large B-cell lymphoma (T-DLBCL), or >2 extranodal sites)

✓ **Investigations**

1) CBC
   - Normocytic normochromic anemia
   - Autoimmune hemolytic anemia rare

- Advanced disease: thrombocytopenia, neutropenia, and leucoerythroblastic anemia

2) Peripheral blood film may show lymphoma cells.
3) Flow cytometry of peripheral blood only if lymphocytosis is present.
4) Increase in uric acid.
5) Abnormal LFTs in liver metastases
6) Increased LDH (rapidly progressing disease and poor prognostic factor)
7) SPEP and immunoglobulin quantitation (screen for high IgM monoclonal protein and hyperviscosity in indolent lymphomas)
8) Staging either by CT neck, chest, abdomen, pelvis, and BM biopsy or PET imaging pre- and post-therapy to ensure post-treatment remission.
9) Definitely diagnosed by:
   - Lymph node biopsy: excisional biopsy preferred, + histopathology & flowcytometry. If mass --> biopsy + histopathology + Immunohistochemistry {IHC}

   - BM biopsy: not optimal for diagnosis as BM is involved in only 30% of high-grade lymphomas (may help of the LNs are not evident while Lymphoma is suspected & CBC is affected).
10) Staging by Ann Arbor Classification protocol
   I. Single lymph node
   II. 2 or more lymph nodes/regions on the same side of diaphragm
   III. Nodes on both sides of diaphragm. The spleen is regarded as a Lymph Node region, so lymphoma with splenomegaly -->Stage III
   IV. Spread beyond lymph nodes.

↳ Each stage may be subdivided into A or B

- A = No systemic symptoms other than pruritus
- B = Weight loss > 10% in last 6 months, fever > 38c, night sweats

✓ **Treatment protocol**

- Indolent NHL, localized disease (e.g., stage I or II)
  - Radiotherapy to primary site and adjacent nodal areas
  - Splenectomy: splenic marginal zone lymphoma
- Goal of treatment in stage 3 or 4 indolent NHL is symptom management:
  - Watchful waiting
  - Radiation therapy for localized symptomatic disease

- Bendamustine plus rituximab, an anti-CD20 Ab, is superior to CHOP and rituximab (R-CHOP) for advanced-stage disease.
- Obinutuzumab (novel anti-CD20 Ab) is superior to rituximab for advanced-stage follicular lymphoma (GALLIUM Trial).

- Aggressive lymphoma: the goal of treatment is curative:
  - Combination chemotherapy: CHOP is the mainstay, plus rituximab if B-cell lymphoma.
  - Radiation for localized/bulky disease
  - CNS prophylaxis with high-dose methotrexate if certain sites are involved (e.g., testes)
  - Relapse, resistant to therapy: high dose chemotherapy, autologous SCT, CAR T cell therapy in 2ndrelapse

- Highly aggressive lymphoma
  - Burkitt lymphoma: short bursts of intensive chemotherapy; "CODOX-M" chemotherapy regimen. Also often used ± IVAC with Rituximab.
  - CNS prophylaxis and tumor lysis syndrome prophylaxis.

✓ **Complications:**

- Hypersplenism
- Infection
- Autoimmune hemolytic anemia and thrombocytopenia
- Vascular obstruction (from enlarged nodes)
- Bowel perforation
- Tumor lysis syndrome (particularly in very aggressive lymphoma); See tumor lysis syndrome.

✓ **Prognosis**

1. Follicular lymphoma: Follicular Lymphoma International Prognostic Index is used: age >60; >4 nodal areas; >6 cm nodal areas; elevated LDH; Lugano stage III-IV; Hb <12 g/dL; high β-2 mi cryoglobulin; BM involvement.
   - based on calculated risk, mean 5-year survival ranges from 53-91%
   - rarely curative, typically relapsing and remitting course with the risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma

2. Diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrod 2-4); elevated LDH; >1extranodal site.
   - based on calculated risk, mean 5 yr survival ranges from 26-73%
   - ~40% rate of cure

✓ **Non-Hodgkin's lymphoma (NHL) (NICE guideline 2016):**

- Include any kind of lymphoma except Hodgkin's lymphomas.
- Most of NHL are of B cell phenotype, although T cell tumors are increasingly being recognized.
- Subtypes of non-Hodgkin's lymphoma (NHL):
  - diffuse large B-cell lymphoma.
  - Burkitt lymphoma.
- Diagnosis
  - Type of biopsy: the first line is Excision biopsy. If not surgically feasible -->needle core biopsy procedure
  - In patients with histologically high-grade B-cell lymphoma, use FISH (fluorescence in situ hybridisation) to identify a MYC rearrangement.
  - If a MYC rearrangement is found --> use FISH to identify the immunoglobulin partner and the presence of BCL2 and BCL6 rearrangements.
  - Indications of using FDG-PET-CT imaging (fluorodeoxyglucose-positron emission tomography-CT)
    i. for Staging
    ii. to assess response at completion of planned treatment for:
      - diffuse large B- cell lymphoma.
      - Burkitt lymphoma.

    iii. to assess response to treatment before autologous stem cell transplantation for high-grade (NHL).
- Management:

Follicular lymphoma:

- Stage IIA --> local radiotherapy as first-line.
- Stage IIA + asymptomatic + single radiotherapy volume is not suitable -->'watch and wait' (observation without therapy).
- Stage IIA + symptomatic + single radiotherapy volume is not suitable -> treat as advanced-stage (stages III and IV) symptomatic.
- Advanced-stage (stages III and IV) asymptomatic --> rituximab.
- Advanced-stage (stages III and IV) symptomatic --> rituximab + combination with:
  - cyclophosphamide, vincristine and prednisolone (CVP)
  - cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
  - mitoxantrone, chlorambucil and prednisolone (MCP)
  - cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon- α(CHVPi) or
  - chlorambucil
- Relapsed or refractory advanced-stage (stages III and IV): induction of remission by Rituximab + combination with chemotherapy. While maintenance therapy by Rituximab monotherapy. In second or subsequent remission by stem cell transplantation

- MALT lymphoma
  - ℛ H. pylori-positive gastric MALT lymphoma -->Helicobacter pylori eradication therapy.
  - ℛ Gastric MALT lymphoma that responds clinically and endoscopically to H. pylori eradication therapy but who have residual disease shown by surveillance biopsies of the stomach, + no high-risk features--> watch and wait (observation without therapy).
  - ℛ Residual MALT lymphoma after H. pylori eradication therapy + high risk of progression [H. pylori-negative at initial presentation or t(11:18) translocation] -->chemotherapy (for example, chlorambucil or CVP) + rituximab OR gastric radiotherapy.
  - ℛ Non-gastric MALT lymphoma
    - localized disease sites -->radiotherapy
    - if radiotherapy is not suitable or disseminated disease -->chemotherapy (for example, chlorambucil or CVP) + rituximab.
    - localized + asymptomatic + radiotherapy is not suitable --> watch and wait (observation without therapy)

- Mantle cell lymphoma:
  - ℛ Advanced-stage (symptomatic) --> chemotherapy + rituximab
  - ℛ Localised stage I or II --> radiotherapy.
  - ℛ Non-progressive + asymptomatic + radiotherapy is not suitable --> 'watch and wait' (observation without therapy)
  - ℛ Chemosensitive mantle cell lymphoma -->autologous stem cell transplantation.
  - ℛ previously untreated + stem cell transplantation is unsuitable --> Bortezomib

✓ **NHL subtypes and cytogenetics**

1) t(1:14): This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates BCL10.

2) t(8;14): seen in Burkitt's lymphoma. MYC oncogene is translocated to an immunoglobulin gene.

3) t(11;14): seen in Mantle cell lymphoma. deregulation of the cyclin D1 (BCL-1) gene

4) t(11; 18). This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates MALT1 .

5) t(14;18): This translocation is associated with follicular lymphoma. It results in a chimeric heavy-chain Ig (chromosome 14) and BCL2 (chromosome 18) gene. This disease presents with painless “waxing and waning” lymphadenopathy in additional to constitutional symptoms.

✓ **Relation of infection to NHLs**

- ❖ Viruses
  - EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
  - HTLV-1: Adult T-cell leukemia/lymphoma
  - HIV-1: High-grade B-cell lymphoma
- ❖ Bacteria
  - Helicobacter pylori: gastric lymphoma (MALT)
- ❖ Protozoa
  - malaria: Burkitt's lymphoma

Burkitt's Lymphoma

- Burkitt's lymphoma is a monoclonal proliferation of B lymphocytes, which results (in approximately 90% of the cases) from chromosome translocations that involve the Myc gene. Chromosome translocation means that a chromosome is broken, which allows it to associate with parts of other chromosomes.
- It is a high-grade B-cell neoplasm.
- There are two major forms:
  1. endemic (African) form: typically involves maxilla or mandible
  2. sporadic form:
     - Abdominal (e.g., ileo-caecal) tumors are the most common form.
     - More common in patients with HIV.
- Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14). The classic chromosome translocation in Burkitt's lymphoma involves chromosome 8, the site of the MYC gene.
- The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.
- Microscopic findings: 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing deadapoptotic tumor cells.
- Management: chemotherapy tends to produce a rapid response which may cause 'tumour lysis syndrome'.
  - ℛ Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin*) is often given before the chemotherapy to reduce

the risk of this occurring. *Allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective

- Complications of tumour lysis syndrome include:
  - Hyperkalaemia
  - Hyperphosphataemia
  - Hypocalcaemia
  - Hyperuricaemia
  - acute renal failure

- Prognosis
  - Localized Burkitt's is associated with around a 90% survival rate.
  - although the prognosis is less good in adults.

Table 35. Characteristics of Select Non-Hodgkin Lymphomas

	Follicular Lymphoma	DLBCL	Burkitt Lymphoma	Mantle Cell Lymphoma
Percentage of NHLs	22-30%	33%	<1% adult NHLs 30% childhood NHLs	6%
Genetic Mutation	Bcl-2 activation	Bcl-2, Bcl-6, Myc rearrangements	c-Myc activation	Overexpression of cyclin D1 (Bcl-1 activation)
Classification	Indolent	Aggressive (high-grade)	Very aggressive	Indolent
Risk Factors	Middle-age – elderly	Previous CLL (Richter's transformation: 5% CLL patients progress to DLBCL)	1. Endemic: African origin, EBV-associated 2. Sporadic: no EBV 3. HIV-related: AIDS-defining illness	Male (M:F=4:1)
Clinical Features	Widespread painless LAD* ± BM involvement Frequent transformation to aggressive lymphoma Very responsive to chemoradiation treatment	Rapidly progressive LAD and extranodal infiltration 50% present at stage I/II, 50% widely disseminated	Endemic form: massive jaw LAD "Starry-sky" histology High-risk of tumour lysis syndrome upon treatment	Often presents as stage IV with palpable LAD Involvement of GI tract (lymphomatosis polyposis), Waldeyer's Ring 5 yr survival 25%

*LAD = lymphadenopathy