Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Lymphomas

Objectives :

- Objectives were not provided

Worked on this lecture:

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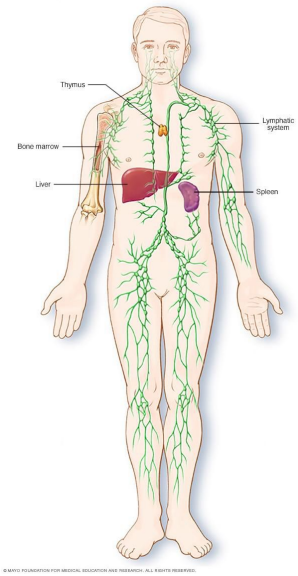
Resources :

Doctors Slides + Notes: Dr. Eyad F. Alsaeed
Books: Step up, Kumar.
Videos: MedEd

Lymphoma

Definition:



Lymphoma is a cancer of the **lymphatic system**, which is part of the body's germ-fighting network that gives us immunity

The lymphatic system includes :

- Lymph nodes (lymph glands)
- Spleen
- Thymus gland
- Bone marrow.

Lymphoma can affect all those areas as well as other organs throughout the body. Lymphatic system is like a tree with many branches that why cancerous cells can easily spread.

The main subtypes are:

- Hodgkin's lymphoma (formerly called Hodgkin's disease)
  - Characterized by the presence of "Reed-Sternberg cells"
- Non-Hodgkin's lymphoma

Symptoms:

- Signs and symptoms of lymphoma may include:
  - Painless swelling of lymph nodes "Non tender Lymphadenopathy" in the neck, armpits or groin , get painful after drinking alcohol. Only in Hodgkin's
  - Persistent fatigue
  - B symptoms:
    - Persistent Fever without infection.
    - Night sweats
    - Unexplained Weight loss and reduced appetite
  - Shortness of breath "Mass symptoms" if the lymph node enlarge in the mediastinum it can cause compression, If it's very large it reaches posterior mediastinum and causes dysphagia
  - Itchy skin "Pruritus"
- Some additional symptoms of **non-Hodgkin** lymphoma include:
  - Persistent coughing
  - Shortness of breath

  → If in the mediastinum
  - Pain or swelling in the abdomen
  - Pain, weakness, paralysis, or altered sensation may occur if an enlarged lymph node presses against spinal nerves or the spinal cord.
- Some symptoms depends on the location and are caused by mass effect
- Lymphoma can spread rapidly from the lymph nodes to other parts of the body through the lymphatic system. As cancerous lymphocytes spread into other tissues, the immune system cannot defend against infections as effectively. NHL spreads **hematologically** and have more organ involvement whereas HL spreads by **continuity** to nearby lymph nodes

WHO Classification of Hematological Neoplasms

- Myeloid
- **Lymphoid**
  - B cell neoplasms
    - Includes plasma cell myeloma
  - T cell neoplasms
  - Hodgkin's lymphoma
- Histiocytic
- Mast Cell

Risk factors:

Risk factors for Hodgkin lymphoma:
• **Infectious mononucleosis:** The Epstein-Barr virus (EBV) can cause mononucleosis. This disease increases the risk of lymphoma. • **Age:** People aged 20-30 years and those 55 years of age have a higher risk of lymphoma. HL has bimodal age distribution (15-30 and >50) • **Sex:** Hodgkin lymphoma is slightly more common in males than females. • **Family history:** If a sibling has Hodgkin lymphoma, the risk is slightly higher. If the sibling is an identical twin, this risk increases significantly. • **HIV infection:** This can weaken the immune system and increase the risk if a HIV patient present with lymphadenopathy you must consider lymphoma
Risk factors for non-Hodgkin lymphoma:
• **Age:** Most lymphomas occur in people aged 60 years and older. However, some types are more likely to develop in children and young adults. • **Sex:** Some types are more likely in women. Men have a higher risk of other types. • **Ethnicity and location:** In the U.S., African American and Asian American people have a lower risk for non-Hodgkin lymphoma than white people. Non-Hodgkin Lymphoma is more common in developed nations. • **Chemicals and radiation:** Nuclear radiation and certain agricultural chemicals have links to non-Hodgkin lymphoma. • **Immunodeficiency:** A person with a less active immune system has a higher risk. This may be due to anti-rejection medications following a solid organ transplant or **HIV**. • **Autoimmune diseases:** This type of disease occurs when the immune system attacks the body's own cells. Examples include rheumatoid arthritis and celiac disease. • **Infection:** Certain viral and bacterial infections that transform lymphocytes, such as the Epstein-Barr virus (EBV), increase the risk. This virus causes glandular fever.

Diagnosis:

Most important thing to know in this lecture is how to diagnose lymphoma***

Swollen lymph nodes

- **History**
  - Non tender lymphadenopathy is the most common symptoms
  - **B symptoms (**Fever, weight loss, Night sweats**)**, PS
  - Must differentiate between malignant lymphadenopathy and:
    - Reactive lymphadenopathy "Infectious".
      - Is it painful ? Lymphoma is non tender
      - Did you had any infection or signs of infection prior to the lymph swelling? E.g. URT symptoms.
      - Did the size of the lymph regress with time? Lymphoma almost never regress in size without treatment it only gets larger.
      - When reactive lymphadenopathy is suspected give ABx if it doesn't respond you move to Bx
    - Autoimmune lymphadenopathy
- **Physical Exam** Must examine every lymph node in the body
  - nodes, liver, spleen, oropharynx
- CBC, Creatinine, liver function tests, LDH, calcium
  - To rule out organ involvement especially with NHL. and to establish a baseline
- **Biopsy pathology review** A biopsy is **required** for diagnosis
  - **Types of biopsy:**
    - Fine needle aspiration
      - Takes only few cells out
      - Tells you there is a malignancy but doesn't tell you what type
      - Never used to diagnose lymphoma
    - Incisional biopsy "True-cut Biopsy "
      - Takes small part of the lymph node
      - We use this for diagnosis
    - Excisional biopsy
      - Take the whole lymph node out
      - Both incisional and excisional are used for diagnosis "Doctor said incisional is better"

- **CT**
  - Neck, thorax, abdomen, pelvis → Done only if the biopsy is +ve for staging
- **Bone marrow aspiration & biopsy**

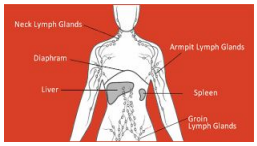
Additional Staging Investigations

- PET or 67Ga scan
  - PET is extremely important to do after staging (Before treatment) and after treatment. Why?
    - Before treatment to see if it would show up positive (5% of the patients don't respond to the PET scan خير شر"false negative") and to establish a baseline.
    - After treatment to check for any residual cancer. PET scan can differentiate between fibrosis/necrosis from treatment, and active cancer
- CT / MRI of head & neck, MRI - CNS, bone, head & neck presentation
- For Gastric lymphoma
  - Cytology of effusions, ascites, Endoscopy,
- Endoscopic U/S
- HIV, CSF cytology - testis, paranasal sinus, periorbital, paravertebral, CNS, epidural, stage IV with bone marrow involvement.

Quick recap:

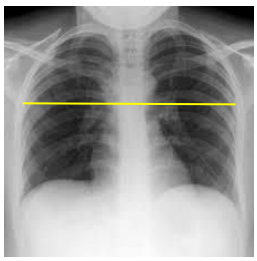
- Take **Hx and physical examination**, you suspect lymphoma you move right away to Incisional/Excisional biopsy for diagnosis. Biopsy is positive and diagnosis is made? You then do a CT scan (neck, thorax, abdomen, pelvis) and Bone marrow Bx for staging. After staging you do a **PET scan before and after Tx**.

The Staging System:



Cotswolds Meeting modification of Ann Arbour Classification:

Consist of a number+letter. It was initially made for HL but now it is used for all lymphomas

I	Single lymph node region (or lymphoid structure) Optimal prognosis
II	2 or more lymph node regions On the same side of the diaphragm
III	Lymph node regions on both sides of diaphragm Above/below
IV	Extensive extranodal disease (more extensive than "E") Metastasis
A	Asymptomatic
B Worsens the prognosis	One of the following is enough: **Fever:** • > 38º, recurrent. **Night sweats:** • Drenching Soaking, recurrent. Brucellosis can also cause drenching night sweats **Weight loss:** • > 10% ideal body weight in 6 months. When a patient comes with B symptoms the whole prognosis/Treatment change, so you must be careful when taking the history. Not every fever, night sweats, weight loss are considered B symptoms they have to follow these characteristic.
X Written only when tumor is large	**Bulky disease** • Mediastinal: ○ ≥ 10 cm or > 1/3 internal transverse diameter at T5/6 Largest diameter of the chest on PA CXR (posteroanterior chest X-ray) • Non mediastinal ○ ≥ 5cm  Example: if the diameter here is 21 cm and the lymph size is 8 cm is it bulky? Yes because its > ⅓ of the diameter.
E	Limited extranodal extension from adjacent nodal site

Examples:

Stage IIA:

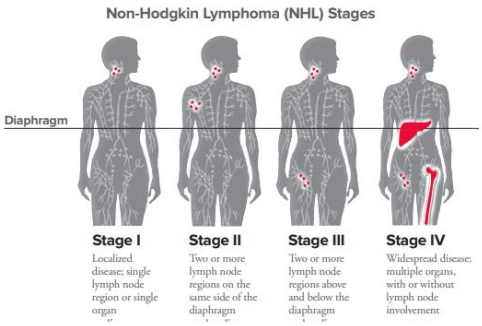
- Asymptomatic patient with ≥ 2 lymph nodes that are both 3cm in size on the same side of the diaphragm.

Stage IBx:

- Patient with B symptoms and one lymph node that is 11 cm in size "Bulky disease".

Stage IIIA:

Asymptomatic patient with one lymph node in his neck and one lymph node in his abdomen "below the diaphragm" that are both 4 cm in size.

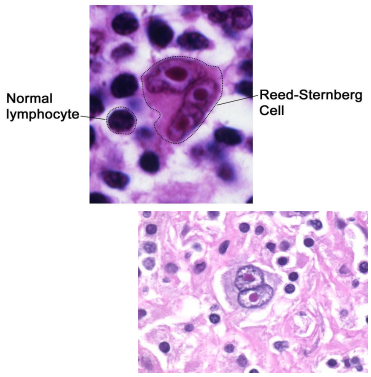


Types and their Treatment:

Doctor said: "No need to know the details of **treatment** for your level just know whether Chemo or radiation or both"*** Focus on what's red regarding treatment

Hodgkin's Lymphoma (= "Hodgkin's disease")

- Characterized by the presence of Reed-sternberg cells in all types Large, neoplastic cell with two or more nuclei, resemble owl's eyes



Types:

1. Nodular lymphocyte-predominant HL
2. Classical HL
   - Nodular sclerosis HL
   - Lymphocyte-rich classical HL
   - Mixed cellularity HL
   - Lymphocyte depletion HL

Very favourable prognosis:

- Stage 1A NLPHL

- Nodular Lymphocyte Predominant HL
  - Usually localized, peripheral nodal sites
  - Good prognosis, but some late relapses (>10yr)

- Stage 1A high neck NS Nodular sclerosis**, LRCHL** Lymphocyte-rich classical HL**.**

Treatment:

- IFRT 35 Gy / 20 (Local radiation only)

Early Stage: **1A, 2A** with no bulk

FAVOURABLE prognosis if:	**UNFAVOURABLE** prognosis if:
1-3 sites Age ≤ 40 ESR < 50 NS, LRCHL	> 3 sites Age > 40 ESR > 50 Mixed cellularity
Treatment	
ABVD X 3 - 4. Then IFRT 30 Gy / 20 (Chemotherapy 3-4 cycles followed by radiation)	ABVD X 4 - 6. Then IFRT 30 Gy / 20 (Chemotherapy 4-6 cycles followed by radiation)

Advanced Stage:

Stage 3, 4, B symptoms, bulky disease

Treatment: (Chemotherapy: 6 cycles if stage A, 8 cycles if stage B. followed by radiation, only if bulky disease or there is residual cancer)

- ABVD X 6 - 8
- IFRT
  - At sites of bulky disease
  - At sites of residual disease (35 Gy / 20)

Patients with HL are at risk for secondary cancer from treatment (breast, lung, skin), Myelodysplastic syndrome in women and CAD.

Types and their Treatment:

Non-Hodgkin's Lymphoma

*Some slides were not included from here. Doctor said: "مو مطالبين فيها"

Clinical Grouping of NHL

1. Indolent
2. Aggressive
3. Highly aggressive

Formerly was:

1. Low Grade
2. Intermediate Grade
3. High Grade

Clinical grouping	Type	Approximate international incidence
Indolent (= "low grade") Very slow growing but rarely cured.	**Follicular lymphoma Grade 1,2** Treatable at stage 1 **t(14;18),** usually peripheral	**22%**
	Marginal zone lymphoma • Nodal • Extranodal (MALT)	 1% 5%
	Small lymphocytic lymphoma	6%
	Lymphoplasmacytic • asociación with Waldenstrom's macroglobulinemia	1%
Aggressive (="intermediate grade")	**Diffuse large B-cell lymphoma**	**21%**
	Primary mediastinal large B cell lymphoma	2%
	Anaplastic large T / null cell lymphoma	2%
	Peripheral T cell lymphoma	6%
	Extranodal NK / T cell lymphoma, nasal type	-
	Follicular lymphoma Grade 3	-
	Mantle cell lymphoma	6%
Highly Aggressive (= "High grade") High recurrence rate	**Lymphoblastic lymphoma**	2%
	Burkitt's lymphoma **t(8;14),** Mainly african children with EBV infection	1%
	Burkitt's like lymphoma	2%

Extra:
Mycosis fungoides is a T-cell lymphoma of the skin, it presents as a skin lesions resembling eczema or psoriasis. Can be treated with topical steroids. When this malignancy spreads to the blood it is called **Sézary syndrome**.

Types and their Treatment:

Indolent Lymphoma: e.g. **Follicular Grad 1-2**, **small lymphocytic**, **marginal zone**

- **Limited Disease**
  (Stage **1A, 2A** if 3 or less adjacent node regions) = local radiotherapy only

  Treatment:
  - IFRT 30-35 GY
    - Involved Field Radiotherapy.
      - 35 Gy for follicular.
      - 30 Gy for Small Lymphocytic and marginal Lymphomas
  - Expect ~ 40% long term FFR
  - Alternate:
    - Chemotherapy
    - Observation.
      - Treat when symptomatic.

- **Advanced Stage** No specific treatment so no questions gonna come from here.
  (some Stage 2, Stage **3, 4**)

  Treatment:
  - Palliative **radiation** therapy for **localized** symptomatic disease
    - IFRT 15-20 Gy / 5
  - Palliative **chemotherapy** for **disseminated** symptomatic disease
    - CVP "Cyclophosphamide, vincristine, prednisone", chlorambucil
  - **Observation** only if **low bulk, asymptomatic**
    - Treat when symptomatic

Aggressive Lymphoma: e.g. Diffuse large B cell

Treatment:

- **Stage I, some Stage II:** (Chemotherapy 3 cycles followed by radiation)
  - CHOP "or CHOP-R" x 3 + IFRT (35-45 Gy) "higher radiation dose if residual" disease
  - Expect ~ 75% long term FFR

- **Stage III, IV**, **B symptoms**, or **bulky disease**
  (Chemotherapy: 6 cycles if stage A, 8 cycles if stage B. followed by radiation, only if bulky disease or there is residual cancer)
  - CHOP or "CHOP-R" x 6-8
  - IFRT (35-45 Gy) to
    - sites of initial bulk
    - residual disease (i.e. PR)

Types and their Treatment:

MALT Lymphoma: Important because its common in saudi arabia especially gastric.

Marginal zone B-cell lymphoma of extranodal (MALT) type

- **Stomach:** associated with Helicobacter pylori infection
- **Salivary Gland:** associated with Sjogren's syndrome
- **Thyroid:** associated with Hashimoto's thyroiditis

→ chronic antigen stimulation

- Orbital (lacrimal, conjunctiva)
- Other: Waldeyer's ring, breast, bladder, lung, skin

- **Gastric MALT Lymphoma treatment:**
  - **Stage IE**: H. pylori +ve
    - PPI, 2 antibiotics (e.g. clarithromycin, amoxicillin) (H.pylori eradication)
    - Follow up gastroscopy with Biopsy every 6 month for 2 yrs, then every 1 year
  - **Stage IE:** H. pylori -ve or antibiotic failure
    - IFRT 30 Gy (95% local control) (Local radiotherapy only)
  - Stage 2 or higher if it spreads around the stomach, give systemic Tx
    - Treat as indolent lymphoma + H. pylori eradication

Quick info:
Chemotherapy regimens used in lymphoma:
- Hodgkin's lymphoma: **ABVD**
- Non-Hodgkin's lymphoma: **CHOP.** in most cases rituximab is added → **CHOP-R**

Summary

<table>
<tr><th colspan="3">Lymphoma
A cancer of the lymphatic system which is part of the body's germ-fighting network</th></tr>
<tr><td></td><td>Hodgkin’s
Characterized by reed-sternberg cells</td><td>Non Hodgkin’s</td></tr>
<tr><td>Risk factors</td><td>EBV, HIV</td><td>EBV, HIV, H.pylori, solid organ transplant immunosuppressants</td></tr>
<tr><td rowspan="2">Symptoms</td><td colspan="2">Painless swelling of lymph nodes, B symptoms (Recurrent Night sweats, recurrent fever, >10% body weight loss over 6 months), fatigue, itching</td></tr>
<tr><td>Lymph node gets painful after drinking alcohol.</td><td>-</td></tr>
<tr><td>Diagnosis</td><td colspan="2">1. History and physical exam
2. Biopsy; Incisional or excisional(No diagnosis without biopsy)
3. CT and Bone marrow biopsy for staging
4. PET scan before and after treatment</td></tr>
<tr><td>Staging</td><td colspan="2">I: Single lymph node
II: ≥ 2 lymph nodes on the same side of the diaphragm
III: ≥ 2 on different sides of the diaphragm
IV: Metastasis

A: Asymptomatic
B: Has B symptoms
X: Bulky disease.
• Mediastinal (> 10 cm or >⅓ internal transverse diameter)
• Non mediastinum (≥ 5 cm)
E: Limited extranodal extension from adjacent nodal site</td></tr>
<tr><td>Chemo Regimens</td><td>ABVD</td><td>CHOP or CHOP-R</td></tr>
<tr><td>Types and treatment</td><td>Very favourable: 1A NLPHL, NS, LRCHL
• Local radiotherapy only

Early: 1A, 2A
• Favourable: 3-4 cycles chemo → radiation
• Unfavourable: 4-6 chemo → radiation

Advanced: Stage 3-4, B symptoms, Bulky disease.
• Chemotherapy 6 cycles if stage A, 8 cycles if stage B → radiation, only if bulky disease or there is residual cancer</td><td>Indolent: Follicular 1-2, SLL, Marginal zone.
• Limited: Local radiation only

Aggressive: Diffuse large B cell
• Stage I, some stage II:
○ 3 cycles Chemo → radiation
• Stage III-IV, B symptoms, Bulky disease:
○ Chemotherapy 6 cycles if stage A, 8 cycles if stage B → radiation, only if bulky disease or there is residual cancer

Gastric MALT:
• Stage IE: H. pylori +ve:
○ H.pylori eradication (ABx+PPI)
• Stage IE: H. pylori -ve or antibiotic failure:
○ Local radiotherapy only
• Stage 2 or higher
○ Treat as indolent lymphoma + H. pylori eradication</td></tr>
</table>

Questions:

1. A 45-year old known male case of Hodgkin's lymphoma stage 2A treated with 3 cycles of chemotherapy followed by involved field radiation therapy, CT scan in follow up reveals 1 cm residual mass at site of treatment. Which ONE of the following is the gold standard test to differentiate between residual disease and fibrosis in such lymph node?
   A. Bone scan
   B. CT scan
   C. Gallium scan
   D. PET scan

2. A 30 year old male patient presented with epigastric pain, dyspepsia, on and off vomiting. He had endoscopy which revealed a mass at the antrum. Biopsy is consistent with MALT Lymphoma. Which one of the following is the initial management plan for this patient?
   A. Antibiotic combination
   B. Chemotherapy
   C. Radiation therapy
   D. Surgical resection

3. Nontender lymphadenopathy made worse with alcohol, what is the diagnosis?
   A. Follicular lymphoma
   B. Gastric MALT Lymphoma treatment
   C. Hodgkin’s lymphoma
   D. Diffuse large B-cell lymphoma

4. A 38-year-old man presented with shortness of breath, CT scan of the chest revealed a 12 cm mediastinal mass. Biopsy consistent with nodular sclerosis Hodgkin's lymphoma. All staging exams were negative. Stage was AIx.Which one of the following is the best choice for management?
   A. Chemotherapy only.
   B. Chemotherapy followed by radiation therapy.
   C. Local Surgical excision of the mass.
   D. Bone marrow transplant

5. A 28-year old male is seen for nontender lymph node. Excisional biopsy is undertaken and the diagnosis of lymphoma is made. A chest X-ray shows a single lymph node in the thorax. The CT scan reveals a single lymph node in the thorax and a single lymph node in the abdomen consistent with lymphoma. What stage is this lymphoma?
   A. Stage II
   B. Stage I
   C. Stage IV
   D. Stage III

6. Which one of the following is the commonest presentation of stage A2 Hodgkin lymphoma?
   A. Fatigue
   B. Fever
   C. Neck mass swelling
   D. Night sweating

1. D
2. A
3. C
4. B
5. D
6. C