433 Teams

MEDICINE

1 | LYMPHOMA

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Objectives:

1. Describe the pathology classification of Lymphoma
2. Describe the Clinical Presentation of Lymphoma
3. Work up lymphoma
4. know the treatment of lymphoma

WHO Classification of Hematological Neoplasms:

Lymphoid	Histiocytic	Myeloid	Mast cell
1-B cell neoplasms (Includes plasma cell myoloma) 2-T cell neoplasms. 3-Hodgkin's lymphoma			

Clinical Grouping of Lymphomas

A. Indolent: = low grade

- ✓ **Follicular lymphoma Grade 1,2 =22%**
- ✓ **Marginal zone lymphoma :**

  -Nodal 1%
  -Extranodal (MALT) 5%
- ✓ **Small lymphocytic lymphoma 6%**
- ✓ **Lymphoplasmacytic* 1%**

***association with waldenstrom's macroglobulinemia**

B. Aggressive: = intermediate grade

- ✓ **Diffuse large B-cell lymphoma = 21%**
- ✓ **Primary mediastinal large B cell lymphoma 2%**
- ✓ **Anaplastic large T / null cell lymphoma2%**
- ✓ **Peripheral T cell lymphoma 6%**
- ✓ **Extranodal NK / T cell lymphoma, nasal type**
- ✓ **Follicular lymphoma Gd 3**
- ✓ **Mantle cell lymphoma 6%**

C. Highly aggressive: = High grade

- ✓ **Lymphoblastic lymphoma 2%**
- ✓ **Burkitts lymphoma 1%**
- ✓ **Burkitt-like lymphoma 2%**

Notes:

*NHL is more common than HL.
*Hodgkin usually present with lymphadenopathy, while NHL extra-nodal (any organ).
*Lymphomas can present with any age group.

Follicular lymphoma:

Grade 1 =0-5/hpf , Grade 2 =6-15\hpf , Grade 3 = >15/hpf

Number of Large cells

- Little clinical difference between Grades 1 and 2
- No difference in treatment of Grades 1 and 2
- Most patients have disseminated disease at diagnosis: Lymph nodes, spleen and bone marrow.
- < 20 % of patients present in Stage I at diagnosis.

Lymphoma – Staging System: Ann Arbour Classification

It has both, numbers and letters (very important)

-Regions are usually determine the stage
-The number of lymph nodes in the region reflects the prognosis but not the stage

I	Single lymph node region(or lymphoid structure) **E.g.** cervical lymph node involvement level 2, 3 and 4 in one side (Stage I since it is only one region)
II	2 or more lymph node regions (above **or** below the diaphragm) E.g. cervical lymph nodes (right and left)
III	Lymph node regions on both sides of diaphragm (Above **and** Below the diaphragm) E.g. cervical and inguinal lymph nodes involvement
IV	Extensive extranodal disease (more extensive then "E")

A	Asymptomatic
B	Fever > 38, recurrent Night sweats: drenching, recurrent Weight loss > 10% body weight in 6 months. One symptom is enough to call it B lymphoma
X	Bulky disease ≥ 10 cm Or > 1/3 internal transverse diameter at T5-T6 on PA CXR.
E	Limited extra-nodal extension from adjacent nodal site.

X-ray is done to measure the highest diameter, which is at T5\T6 level, and we ask the pt to take deep inspiration and then we measure the diameter

Notes:

*Indolent: very slow growing, difficult to cure, but Symptoms can be controlled.
*Aggressive NHL progress fast, curable, responds very well to treatment (pt may have tumor lysis syndrome)
* Very aggressive we start the treatment before staging.
* Sweating in lymphomas is as if they jumped in the pool "drenching sweat".
*X is divided: Thoracic "or mediastinal" and extra-thoracic

Essential Staging Investigations:

- History – B symptoms, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- Biopsy – pathology review
- CBC
- creatinine, liver function tests, LDH, calcium
- Bone marrow aspiration & biopsy
- CT neck, thorax, abdomen, pelvis

Additional Staging Investigations:

- PET or 67Ga scan (This is for the residual after treating the patient.)
  Order it prior to the treatment
- CT / MRI of head & neck
- Cytology of effusions, ascites
- Endoscopy
- Endoscopic U/S — Gastric lymphoma
- MRI - CNS, bone, head & neck presentation
- HIV
- CSF cytology - testis, paranasal sinus, peri-orbital, paravertebral, CNS, epidural, stage IV with bone marrow involvement.

In Clinical Practice:

When patient present to you with lymphadenopathy you have to take a good history and do physical examination

DDx: 1- Benign causes: Infection > tender and red + source of infection "URTI" + increase "fast" and decrees in size + respond to antibiotic

2-malignant: do core biopsy (you will read in some books that they do excisional biopsy but the doctor said (not used anymore so do not use excisional biopsy)

-PET is highly specific and sensitive 95%, but not found in every hospital "expensive". Gallium is less (60%-70% specific and sensitive), and I expect it will be positive but if it is negative "false negative result" so will not be used for follow-up.

NOTE:

-Metastatic: Thyroid tumor + nasopharyngeal carcinoma associated with "Epstein-Bar virus"

-Systemic diseases can cause Lymphoma: HIV & SLE

-Drug-induced Lymphadenopathy: Phenytoin and some diuretics.

International Prognostic Index for NHL: (important)

Risk factors	
Age	> 60
Stage	3, 4
PS performance status	ECOG ≥ 2 Eastern Cooperative Oncology Group score
LDH	> normal
Extranodal	> 1 site

	Number of Risk Factors	5 yr OS* Overall survival
Low Risk	0-1	75%
Low-Intermediate	2	51%
High-Intermediate	3	43%
High Risk	4-5	26%

Management of NHL: VERY IMPORTANT

INDOLENT	Limited: 1-Asymptomatic: observe 2- Stage 1A, 2A if 3 or less adjacent node regions: chemotherapy +Involved field radiotherapy (IFRT) Use 35 Gy for follicular. 30 Gy for SLL, marginal"	Advanced: some Stage 2, Stage 3, 4 Observation only if low bulk,asymptomatic Treat when symptomatic: 1-Palliative *IFRT for localized symptomatic disease: 2-Palliative chemotherapy (*CVP, chlorambucil) for disseminated symptomatic disease
Aggressive	Stage I, some Stage II " Mainly chemotharaby BUT if it's localized or bulky followed by radiation	- Stage III, IV, B symptoms also burkitts lumphoma Only chemotherapy (*CHOP)
	after he finished the course of treatment and you did PET scan which showed residual **give aggressive chemotherapy**	
Extranodal	•Same treatment as nodal lymphoma Notable Exceptions: • Gastric MALT • Testis • CNS • Skin	

***CHOP :** Cyclophosphamide / Hydroxydaunorubicin / Oncovin (vincristine) / prednisone.
*** IFRT:** Involved-Field Radiation Therapy.
***CVP:** Cyclophosphamide, Vincristine, Prednisone (Chemotherapy Regimen).
***SLL:** Small Lymphocytic Lymphoma.
***MALT:** Mucosa associated lymphoid tissue.

MALT lymphoma:

- Most localized (Stage I, II)
- History of chronic antigen stimulation:
  -Autoimmune disease e.g. Sjogren's, Hashimoto's
  -H. pylori infection

- Stomach
- Lung
- Ocular adnexa
- Thyroid
- Salivary glands

} Most low grade lymphomas at these sites are MALT type

- **Extranodal marginal zone B cell lymphoma of MALT type:**

Presumed to arise in mucosa associated lymphoid tissue (MALT)

- **Gastric MALT Lymphoma:**

- ~ ½ of gastric lymphomas
- association with: -chronic gastritis
  -helicobacter pylori infection

Treatment:

Local treatment for Localized disease

- Radiotherapy :local / regional: 30 Gy / 20
- surgery
- antibiotics for gastric MALT lymphoma
  (amoxicillin-clarithromyccin)
- cyclophosphamide / chlorambucil

Disseminated disease

- ~ 30 % of cases
- Treatment similar to Stage III, IV follicular lymphomas

NOTE:

We don't treat lymphoma with surgery except in gastric lymphoma with obstruction

Testis Lymphoma:

- usually aggressive histology
- elderly patients, less tolerant of chemo
- high risk relapse ∴ need aggressive Treatment
- High risk of:
    - Extra-nodal relapse
    - contralateral testis relapse > 40% by 15yrs
    - CNS relapse > 30% 10yr actuarial risk

Treatment:

All patient

- Orchiectomy (diagnostic & therapeutic)
- CHOP-R x 6
- Scrotal radiation 30 Gy / 15
    - reduces risk testis recurrence to < 10%

Stage 2

- involved field nodal RT

Stage 3+4

- CNS chemoprophylaxis: intrathecal MTX

Lymphoma Follow-up:

- Hx, Px q3mo for 2 yrs, then q6mo to 5 yrs and then annually.
- CBC, LDH
- CT chest, abdo, pelvis q6mo to 5 yrs
- TSH at least annually after neck irradiation
- Breast cancer screening for women treated with chest radiation 10 yrs post RT

Hodgkin's Lymphoma (≡ Hodgkin's disease):

Nodular lymphocyte-predominant HL*	Classical HL
_____	• Nodular sclerosis HL • Lymphocyte-rich classical HL* • Mixed cellularity HL • Lymphocyte depletion HL

Staging Investigations:

- Biopsy – pathology review
- History – B symptoms, pruritis, alcohol pain, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- CBC, ESR
- creatinine, liver function tests, LDH, calcium, albumin
- Bone marrow aspiration & biopsy
  - if abnormal CBC, Stage 2B or higher
- CT thorax, abdomen, pelvis

Other Investigations:

- PET scan
- 67Ga scan
- Lymphangiogram – if expertise available, no PET
- Pregnancy test
- oophoropexy / semen cryopreservation - if chemotherapy or pelvic RT
- Dental assessment – if oropharyngeal RT

Hodgkin's Lymphoma

	Early Stage 1A, 2A		Advanced
	FAVOURABLE 1-3 sites, Age ≤ 40 , ESR ≤ 50 , NS, LRCHL	UNFAVOURABLE > 3 sites, Age > 40 , * ESR > 50 , Mixed cellularity *(Erythrocyte Sedimentation Rate)	-III, IV -Bulky Disease -B Symptoms
Treatment	Chemotherapy(ABVD) + radiotherapy(IFRT)		Mainly chemotherapy (ABVD) Add IFRT if it's -bulky -residual disease

Important note

The difference between NHL and HL in treatment of residual

NHL: aggressive chemotherapy

NH: radiotherapy (IFRT)

ABVD IV **Days 1, 15**

1-Adriamycin(doxorubicin)
2-Bleomycin
3-Vinblastine
4-Dacarbazine

Hodgkin's Lymphoma Rough Approximation of Prognosis:

	FFS	OS
Early	**80 – 90%**	**85 – 95%**
Advanced	**40 – 80%***	

If RT only (STNI): Deaths from 2nd malignancy > deaths from Hodgkin's disease by 15-20yrs

Difference between HL and NHL	
HL	**NHL**
Local,stage I and II in 80-90%	**Stage III and IV in 80-90%**
Center around cervical area	**Disseminated**
Reed-strenberg cells on pathology	_____
Pathologic classification: -lymphocyte predominant has best prognosis -lymphocyte depleted has the worst prognosis	**Pathologic classification:** Burkitt and immunoblastic have worst prognosis

Tumor lysis syndrome (TLS) occurs as a result of massive lysis of malignant cells and release of intracellular contents into the systemic circulation. TLS is most commonly present after initiation of anticancer therapy. It can lead to
1-hyperuricaemia (,causing a painful gout-like condition+ buildup of uric acid in the kidneys can cause damage and stones to form)
2-hyperkalaemia (causing cardiac arrhythmias)
3-hyperphosphataemia (lead to kidney failure)
4-hypocalcaemia (seizures)

Questions

Q1. A 38-year-old woman presents with repeated episodes of sore throat. She is on no medications, does not use ethanol, and has no history of renal disease. Physical examination is normal. Hgb is 9.0 g/dL, MCV is 85 fL (normal), white blood cell count is 2000/µL, and platelet count is 30,000/µL. Which of the following is the best approach to diagnosis?

a. Erythropoietin level.
b. Serum B12.
c. Bone marrow biopsy.
d. Liver spleen scan.
e. Therapeutic trial of corticosteroids.

Q2. A 43-year-old woman complains of fatigue and night sweats associated with itching for 2 months. On physical examination, there is diffuse nontender lymphadenopathy, including small supraclavicular, epitrochlear, and scalene nodes. CBC and chemistry studies (including liver enzymes) are normal. Chest x-ray shows hilar lymphadenopathy. Which of the following is the best next step in evaluation?

a. Excisional lymph node biopsy.
b. Monospot test.
c. core biopsy.
d. Serum angiotensin-converting enzyme level.
e. Percutaneous aspiration biopsy of the largest lymph node.

Q3. A 19-year-old woman presents for evaluation of a nontender left axillary lymph node. She is asymptomatic and denies weight loss or night sweats. Examination reveals three rubbery firm nontender nodes in the axilla, the largest 3 cm in diameter. No other lymphadenopathy is noted; the spleen is not enlarged. Lymph node biopsy, however, reveals mixed-cellularity Hodgkin lymphoma. Liver function tests are normal. Which of the following is the best next step in evaluation?

a. Bone marrow biopsy.
b. Liver biopsy.
c. Staging laparotomy.
d. Erythrocyte sedimentation rate.
e. CT scan of chest, abdomen, and pelvis.

Q4. A 62-year-old woman has noted fever to 38.3°C (101°F) every evening for the past 3 weeks, associated with night sweats and a 15-lb weight loss. Physical examination reveals matted supraclavicular lymph nodes on the right; the largest node is 3.5 cm in diameter. She also has firm rubbery right axillary and bilateral inguinal nodes. Excisional biopsy of one of the nodes shows diffuse replacement of the nodal architecture with large neoplastic cells, which stain positively for B-cell markers. No Reed-Sternberg cells are seen. Which statement most accurately reflects her prognosis?

a. This is an indolent process, which will respond to corticosteroids.
b. This is an aggressive neoplasm, which responds poorly to chemotherapy and will likely be fatal in 6 months or less.
c. This is an aggressive neoplasm, but it may be cured with chemotherapy in up to 60% of the cases.
d. The neoplasm often responds to chemotherapy but usually relapses.
e. Radiation therapy is curative.

Answers: C, C, E, C.

Explanations

A1. This patient has an unexplained pancytopenia. If all three elements (red blood cells, white blood cells, and platelets) are affected, the cause is usually in the bone marrow (although peripheral destruction from hypersplenism can cause pancytopenia as well). In this patient without a history of liver disease or palpable splenomegaly on physical examination, a bone marrow production problem is the most likely culprit.

A2. The long-term nature of these symptoms, the fact that the nodes are non-tender, and their location (including scalene and supraclavicular) all suggest the likelihood of malignancy. And as the doctor said (excisional biopsy not used anymore so do core biopsy)

A3. The staging of Hodgkin disease is important so that proper treatment can be planned. Stage I (single lymph node bearing area) or stage II (more than one lymph node site on the same side of the diaphragm) patients with good prognostic features may be treated with radiation therapy. Those with stage III (affected lymph nodes on both sides of the diaphragm) or stage IV (extra-nodal disease) are treated with combination chemotherapy. CT or MRI of the abdomen and pelvis will show evidence of lymph node involvement below the diaphragm.

A4. This is a classic presentation of diffuse large cell lymphoma. These neoplasms usually present with a rapidly enlarging nodes and B symptoms (fever, night sweats, > 10% weight loss). Extra-nodal disease (eg, gastric involvement) is occasionally seen, whereas extra-lymphatic disease is unusual in the more indolent small cell lymphomas. Although Hodgkin disease can also present in this fashion, the histological features and B-cell markers are those of a non-Hodgkin lymphoma. Untreated large cell lymphomas are progressive and rapidly fatal. Usually, however, they respond to combination therapy (multidrug chemotherapy, often combined with the anti-CD 20 antibody rituximab).

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