Lymphoma

by Dr. Eyad AlSaeed

Note: Doctor said that the slide is more than enough for exam!

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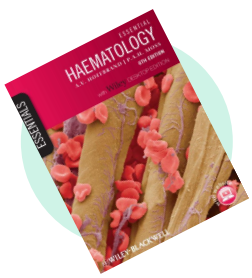
Objectives:

- **Not given yet!**

References:
Slides - Black
Doctor's notes - Red
Step up / davidson - Blue
Extra explanation - Grey
Master the boards - Purple
Pathoma - Dark blue

Optional:



Chapter 19, 20

Editing file

WHO Classification of Hematological Neoplasms

- Myeloid
- Lymphoid (B cell neoplasms (including plasma cell myeloma), T cell neoplasms, Hodgkins)
- Histiocytic
- Mast cell

Lymphoma introduction

- Neoplastic proliferation of lymphoid cells "lymph-" that forms a mass "-oma".
- It has 2 broad categories:
  - Hodgkin disease (حبيب)
  - Non-Hodgkin lymphoma (NHL) (more common & more aggressive)
- Typical presenting symptoms: persistent painless adenopathy and B symptoms (Fever, night sweats and weight loss)
- Typical physical findings: Lymphadenopathy and hepatosplenomegaly

Lymphoma site	Typical presenting symptoms *Medicine recall
CNS lymphoma	Headache, altered mental status, and focal neurologic findings
Waldeyer's ring (ring of lymphoid tonsillar tissue in the oropharynx)	Sinusitis and earaches
Mediastinal lymphoma	Cough, SOB, chest pain, and hemoptysis
Abdominal lymphomas	Abdominal pain, nausea, vomiting, and back pain

Non-Hodgkin Lymphoma

General characteristics

Step-up

- NHL is a diverse group of solid tumors which occurs with the malignant transformation and growth of B or T lymphocytes or their precursors in the lymphatic system.
- The course of the disease and its prognosis are determined by:
  - The type of lymphocyte involved
  - Level of differentiation
- B-cell lymphomas are more common than T-cell lymphomas
- Overall incidence increases with age
- NHL and CLL are extremely similar, but NHL is a solid mass and CLL is "liquid".

Risk factors

Step-up

- Infections
  - HIV
  - Certain viruses (eg. EBV, HTLV-1 (Human T-lymphotropic virus))
  - H.pylori gastritis (risk of 1ry associated gastric lymphoma)
- Immunity
  - Immunosuppression (eg. organ transplant recipients)
  - Autoimmune disease (eg. Hashimoto thyroiditis or Sjögren syndrome → risk of MALT)
- Genetic factors

Classification (details will be discussed later)

Non-Hodgkin Lymphoma

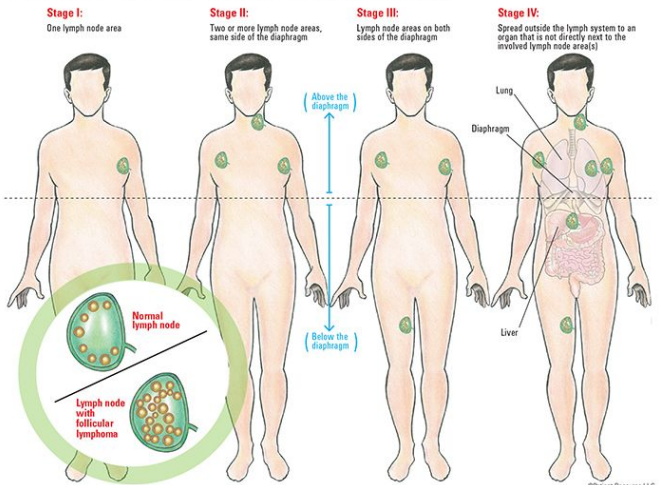
Indolent (low grade)	Aggressive (intermediate grade)	Highly aggressive (high grade)
– Follicular lymphoma Grade 1,2 – Marginal zone lymphoma •Nodal •Extranodal (MALT) – Small lymphocytic lymphoma – Lymphoplasmacytic* *Red = commonest type	– Diffuse large B-cell lymphoma – Primary mediastinal large B cell lymphoma – Anaplastic large T / null cell lymphoma – Peripheral T cell lymphoma – Extranodal NK / T cell[1] lymphoma, nasal type – Follicular lymphoma Gd 3 – Mantle cell lymphoma	– Lymphoblastic lymphoma – Burkitts lymphoma – Burkitt-like lymphoma

[1] T-cell lymphoma is always bad (bad response to chemo.)

Lymphoma - staging system (Ann Arbor system)

"you won't be asked to stage in the exam"

I. **Single lymph node region (or lymphoid structure)** eg. supraclavicular and neck lymph nodes
II. **2 or more lymph node regions** eg. supraclavicular and infraclavicular lymph nodes
III. **Lymph node regions on both sides of diaphragm**
IV. **Extensive extranodal disease (more extensive than 'E')** positive bone marrow → stage IV



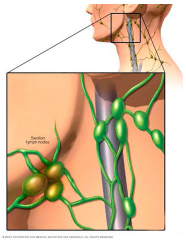
Lymphoma - staging system subscripts (you have to know this)

A	**Asymptomatic**	
B[1]	**Fever**	**> 38°, recurrent**
	Night sweats	**drenching, recurrent**
	Weight loss	**> 10% body wt in 6 months**
X	**Bulky disease** when do we consider it bulky?	**mediastinal: ≥ 10cm, or** **> 1/3 internal transverse diameter @ T5/6 on PA CXR** يعني إذا كان قطر الورم بالنسبة لقطر الـchest أكثر من الثلث **Non-mediastinal: > 5-6 cm**
E	**Limited extranodal extension from adjacent nodal site**	

[1] one symptom is enough to consider it a 'B'

Clinical features

Step-up

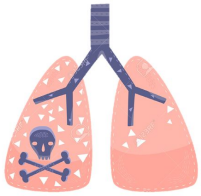


Lymphadenopathy
Painless, firm, mobile, not warm, not red

B-symptoms less common than in Hodgkin

Hepatosplenomegaly abdominal pain, or fullness

Recurrent infections, symptoms of anemia, or thrombocytopenia (due to bone marrow involvement)



Other findings superior vena cava obstruction, respiratory involvement, bone pain, skin lesions

Essential staging investigations

- Biopsy – pathology review
  - biopsy types:
  - Fine needle biopsy → good for leukemia
  - Excisional biopsy → best initial diagnostic test for lymphoma
- History – B symptoms, Performance status
- Physical Exam – nodes, liver, spleen, oropharynx
- CBC (normal in most cases)
- creatinine, liver function tests, LDH, calcium
- Bone marrow aspiration & biopsy
- CT neck, thorax, abdomen, pelvis

Additional staging investigations

- PET or ^{67}Ga scan
- CT / MRI of head & neck
- Cytology of effusions, ascites
- Endoscopy
- Endoscopic U/S } for 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

If a patient presented with a lymph node enlargement, what are the steps that you should follow?
1- Take history: commonest → lymph nodes in the neck
2- Always think of non-malignant causes (eg. benign infection of the tonsils → presents as sore throat, painful nodes)
Other causes might be: chronic inflammation, connective tissue disease, drug induced, or malignancy
3- Examination.
4- If the history and examination were not clear and there's a painless lump, what should the work up be?
- CBC (if WBCs are high → suspect infection, if low → suspect immunosuppression), creatinine, LFTs, etc..
- CT scan (start by the suspected region)
- Excisional (true cut) biopsy

5- If you suspect infection, do NOT perform biopsy or CT scan. Give antibiotics and wait. If it persists more than 4 weeks → perform biopsy and CT scan

PET scan and ^{67}Ga scan

- PET scan is a very sensitive modality (detects 90% of cases)
- Fluorodeoxyglucose (FDG) is a tracer used with PET and has high affinity to malignant cells
- PET scan can be +ve in the following conditions: malignancy, infection, & high glucose level; thus it should NOT be used if you're suspecting infection or if the pt. has ↑ glucose as it might mislead you. In other words, NEVER perform it until you're sure it's a malignancy.
- PET scan should be performed from the beginning if you're sure that patient has lymphoma.
- PET scan is used for follow up to check recurrences of the disease. If PET ain't available Gallium scan can be used but it should be performed before treatment. If gallium was +ve before treatment of the diagnosed lymphoma it can be used for follow up, if not, it can't be used.

International Prognostic Index (IPI) for Diffuse large B-cell lymphoma "you have to know it"

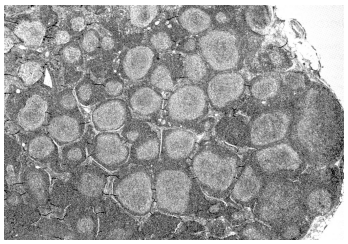
APpLES	
Age	> 60
Performance status (PS)	ECOG[1] ≥ 2
LDH[2]	> normal
Extranodal	> 1 site
Stage	3, 4

Interpretation	Number of risk factors	5 year overall survival(OS)
Low risk	0-1	75%
Low - intermediate	2	51%
High - intermediate	3	43%
High risk	4-5	26%

[1] ECOG (Eastern Cooperative Oncology Group) is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis (i.e. performance status)
[2] Lactate dehydrogenase (LDH)

Indolent Lymphoma (Low grade)

Follicular Lymphoma BCL2



- Proliferation of small B-cells (CD20⁺) that form follicle like nodules
- Mean age of onset is 55 (late adulthood)
- May transform into diffuse, large cell
- translocation: t(14;18) Fourteen starts with 'F'- Follicular
- BCL2 on ch.18 translocates to the IgG heavy chain locus on ch.14
- Most patients have disseminated disease at diagnosis:
  - Lymph nodes, spleen, bone marrow
  - < 20 % Stage I at diagnosis
- Grade (number of large cells):
  - Grade 1 → 0-5/hpf Grade 2 → 6-15/hpf Grade 3 → ≥ 15
- Little clinical difference between Grades 1 and 2
- No difference in treatment of Grades 1 and 2
- NB: grade 1 and 2 are indolent while grade 3 is aggressive

Marginal Zone Lymphoma

- Proliferation of small B-cells (CD20⁺) that expands the marginal zone
- Associated with chronic inflammatory states such as: Hashimoto thyroiditis, Sjögren syndrome, and H. pylori gastritis
- MALToma (Mucosa Associated Lymphoid Tissue) is marginal zone lymphoma in mucosal sites
- Most low grade lymphomas at the following sites (stomach, lung, ocular adnexa, thyroid, salivary glands) are MALT type
- Most MALT lymphomas are localized (Stage I, II)

Mantle Cell Lymphoma

- Proliferation of small B-cells (CD20⁺) that expands the mantle zone
- Presents in late adulthood
- translocation: t(11;14). Cyclin D1 translocates IgG heavy chain locus

Mantlle cell: 11;14 → lowercase 'L' looks like a 1 for 11

Extranodal Lymphoma (includes MALT & testis lymphoma)

Testis Lymphoma

- usually aggressive histology
- elderly patients, less tolerant of chemo
- high risk relapse / need aggressive Tx

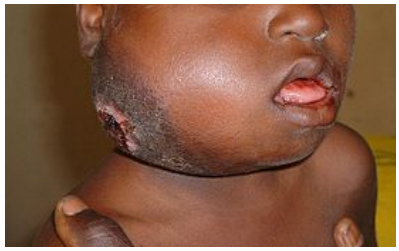
High risk of:

- extranodal relapse
- contralateral testis relapse > 40% by 15 yrs
- CNS relapse > 30% 10 yr actuarial risk

Diffuse large B-cell lymphoma DLBCL (Aggressive) (most common NHL type!)

- Proliferation of large B-cells ($CD20^+$) that grow diffusely in sheets
- Middle-aged and elderly patients
- Locally invasive; presents as large extranodal mass
- High cure rate with CHOP therapy

Burkitt Lymphoma (Highly aggressiv



- Proliferation of B-cells ($CD20^+$)
- More common in children
- Two types:
  - Endemic (African) variety → involves facial bone and jaw
  - Sporadic variety → often involves abdominal organs
- African variety is associated with Epstein-Barr virus (EBV)
- Associated with specific translocation: t(8;14) 8:14 = 8urk14 → uppercase B looks like an 8 (14 = it)
- Translocated c-myc oncogene to the IgG heavy chain locus
- 'starry-sky' appearance on microscopy

NHL Treatment :D في قشرة بندق

(no need to know the details mentioned in the lecture)

- Indolent forms of NHL are not curable but have high 5-year survival rate
- Intermediate and high grade NHLs may be curable with aggressive treatments
- Extranodal lymphoma gets the same treatment as nodal lymphoma EXCEPT: gastric MALT, testis, CNS, skin
- Lymphoma is NEVER treated by surgery unless it caused obstruction
- Local disease (stage Ia): small dose/course of chemotherapy followed by local radiation
- Advanced disease (stage II, III and IV, any "B" symptoms): chemotherapy without radiation (combined with CHOP and rituximab)
  - C = cyclophosphamide
  - H = adriamycin (doxorubicin or "hydroxydaunorubicin")
  - O = vincristine (oncovin)
  - P = prednisone

- Gastric MALT lymphoma is treated with antibiotics (clarithromycin and amoxicillin)
- MALT lymphoma in other sites (not gastric) is treated like any other NHL
- "You won't be asked to stage the disease in the exam, but you need to know the treatments for each"
- Rituximab: Chimeric anti-CD20 monoclonal Ab
  - Mouse variable region & Human constant region (I_gG_1)
  - Direct antitumor effects
    - Complement-mediated cytotoxicity
    - Antibody dependent cellular cytotoxicity
  - Synergistic activity with chemotherapy

Anime fans, guess who's that?! This is to remind u of "CHOP" therapy

Hodgkin Lymphoma

Reed-sternberg cells!

Classification

- 1.Nodular lymphocyte-predominant HL
- 2.Classical HL:

Nodular sclerosis HL
- bands of collagen envelope RS cells in lake-like spaces (lacunar cells)
- Most common subtype
- more in women :o(

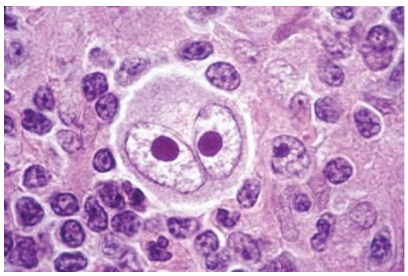
Lymphocyte-rich classical HL
- few Reed-Sternberg cells and many B-cells
- Best prognosis

Mixed cellularity HL
- Large numbers of Reed-Sternberg cells in a pleomorphic background
- abundant eosinophils

Lymphocyte depletion HL
- Lacking in mix of reactive cells
- Worst prognosis

Staging investigations

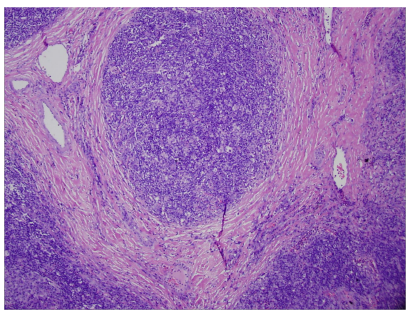
- Biopsy – pathology review
- History – B symptoms, pruritis, alcohol pain, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- CBC, ESR
- creatinine, liver function tests, LDH, calcium, albumin
- Bone marrow aspiration & biopsy
- –if abnormal CBC, Stage 2B or higher
- CT thorax, abdomen, pelvis



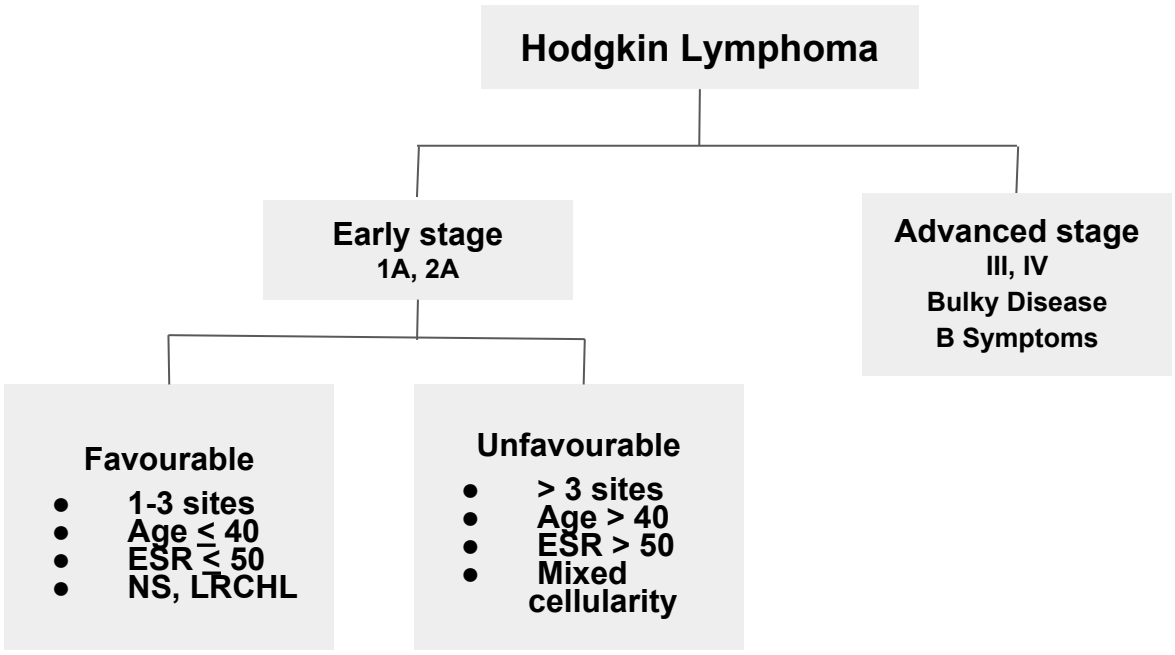
Reed-Sternberg (RS) cells, which are large B-cells with multilobed nuclei and prominent nucleoli **'owl-eyed nuclei'**

Other investigations

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



Nodular sclerosis HL



Hodgkin lymphoma treatment

- **Stage IA, IIA → small dose/course of chemotherapy followed by local radiation** (remember that in NHL radiotherapy is only for stage I while in Hodgkin it's for I and IIA)
- **Stage III, IV → Chemotherapy only (ABVD)** (check the grey box below)

Treatment (the doctor skipped those details)

	Prognosis	Treatment
Early stage HL	Very favourable •Stage 1A NLPHL* •Stage 1A high neck NS, LRCHL	IFRT 35 Gy / 20 *Nodular Lymphocyte Predominant HL usually localized, peripheral nodal sites good prognosis, but some late relapses (>10yr)
	Favourable	•ABVD X 3 - 4 •IFRT 30 Gy / 20
	Unfavourable	•ABVD X 4 - 6 •IFRT 30 Gy / 20 NB: Overlap with favourable prognosis
Advanced stage HL Stage 3, 4, B symptoms, bulky disease	•ABVD X 6 – 8* •IFRT –sites of bulky disease –sites of residual disease (35 Gy / 20) * ABVD until 2 cycles past maximum response	

Other treatment options for favourable prognosis

- STNI Mantle + Para-aortic nodes,spleen 35 Gy/20
  - historical gold standard
  - survival º CMT
  - use if CTx contraindicated
  - but: high risk late toxicity
- ABVD x 2 + IFRT
- ABVD x 6

ABVD:
- doxorubicin (Adriamycin)
- Bleomycin → causes lung fibrosis
- Vinblastine
- Dacarbazine

Tumor Lysis Syndrome (step-up) Important

- This is a potential complication of chemotherapy seen in acute leukemia and high-grade NHL (Burkitt lymphoma patients receiving chemotherapy should be monitored)
- Rapid cell death with release of intracellular contents causes hyperkalemia, hyperphosphatemia and hyperuricemia
- Treat as medical emergency Don't wait

NHL and HL Comparison: (Pathoma)

	Non-Hodgkin Lymphoma	Hodgkin Lymphoma
Overall frequency	60% (more common)	40%
Malignant cells	Lymphoid cells	Reed-sternberg cells
Composition of mass	Lymphoid cells	Predominantly reactive cells (inflammatory cells and fibrosis)
Clinical	Painless lymphadenopathy, usually arises in late adulthood	Painless lymphadenopathy occasionally with 'B' symptoms, usually arises in young adults
Spread	Diffuse; often extranodal	Contiguous; rarely extranodal
Leukemic phase	Occurs	Does not occur

Bone Marrow Transplant

A bone marrow transplant is a medical procedure performed to replace bone marrow that has been damaged or destroyed by disease, infection, or chemotherapy. This procedure involves transplanting blood stem cells, which travel to the bone marrow where they produce new blood cells and promote growth of new marrow.

Autologous Transplant

Autologous transplant involves the use of a person's own stem cells.
They typically involve harvesting your cells before beginning a damaging therapy to cells like chemotherapy or radiation. After the treatment is done, your own cells are returned to your body. This type can only be used if you have a healthy bone marrow. However, it reduces the risk of some serious complications, including Graft Versus Host Disease (GVHD).

Allogeneic Transplant

Allogeneic transplants involve the use of cells from a donor. The donor must be a close genetic match. Often, a compatible relative is the best choice, but genetic matches can also be found from a donor registry.
Allogeneic transplants are necessary if you have a condition that has damaged your bone marrow cells (such as leukemia). However, they have a higher risk of certain complications, such as GVHD. You'll also probably need to be put on medications to suppress your immune system so that your body doesn't attack the new cells. This can leave you susceptible to illness.
The success of an allogeneic transplant depends on how closely the donor cells match your own.

Treatment (This table is for the sake of completeness, you can skip it)

	Stage	Treatment
Indolent Lymphoma e.g. Follicular Gd 1/2, small lymphocytic, marginal zone	Limited disease (Stage 1A, 2A if 3 or less adjacent node regions)	• Involved Field Radiotherapy (IFRT) 35 Gy for follicular. 30 Gy for SLL, marginal • Expect ~ 40% long term FFR • Alternate: CMT & Observation. • Treat when symptomatic.
	Advanced stage	• Palliative RT* for localized symptomatic disease • Palliative chemotherapy** for disseminated symptomatic disease • Observation only if low bulk, asymptomatic – Treat when symptomatic
Aggressive Lymphoma e.g. Diffuse large B cell	Stage I, some stage II	• CHOP* x 3 + IFRT (35-45 Gy)** Expect ~ 75% long term FFR
	Stage III, IV, B symptoms, or bulky disease	CHOP x 6-8 IFRT (35-45 Gy) to - sites of initial bulk - residual disease (i.e. PR)
MALT Lymphoma	Localized disease	•radiotherapy – local / regional: 30 Gy / 20 • surgery • antibiotics for gastric MALT lymphoma • cyclophosphamide / chlorambucil
	Disseminated disease	~ 30 % of cases • Treatment similar to stage III, IV follicular lymphomas
Testis Lymphoma	All patients	• Orchidectomy (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

•History, physical examination every 3 months (q3mo) for 2 yrs, then every 6 months (q6mo) for 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

MCQ’s

Q1: An African child develops massive unilateral enlargement of his lower face in the.'vicinity of the mandible. **Biopsy demonstrates sheets of medium-sized blast cells with admixed Larger macrophages. This type of.tumor has been associated with which of the (.flowing?**
(A) Epstein-Barr virus and t(8:14)
(B) Hepatitis Band t(9j22)
(C) Herpesvirus and CDS
(D) HIV and CD4
(E) Human papillomavirus and t(2;5)
Q2:A 57-year-old man presents with painless swelling in his neck. Physical examination is remarkable for splenomegaly. Biopsy of the neck, mass reveals a neoplasm containing small, cleaved .cells that recapitulate the normal follicular architecture of lymph nodes. Which
of the following mechanisms is most likely involved in the development of this patient’s neoplasm?
(A) Amplification of L-myc
(B) Homozygous loss of p53
(C) Overexpression of bcl-2
(D) Point mutation in ras decreasing its GTPase activity
(E) Reciprocal translocation between chromosome 9 and 22
Q3:A 24-year.old man underwent treatment for Hodgkin lymphoma 1 year ago. He- presents with increasing dyspnea and cough. Physical exam is remarkable for rales bilaterally. Arterial blood gases show hypoxia, and bilateral pulmonary infiltrates are seen on chest x-ray. .which of the following chemotherapeutic agents most likely produced these side effects?
(A) Bleomycin
(B) Cyclophosphamide
(C) Doxorubicin
(D) Vincristine
(E) 5-Fluorouracil
Q4:A 19-year-old w.man is evaluated because of a 6-week history of intermittent low-grade fever, weight loss, and night sweats. On physical examination she is found to have enlarged lymph nodes on both jugular chains and supraclavicular areas, and chest CT scan shows a large mediastinal mass. One of the most accessible cervical nodes is excised surgically for biopsy؛ the pathologist reports the presence of Reed-Sternberg cells. Abdominal CT scan is nondiagnostic and bone marrow biopsy is positive. Which of the following is the most appropriate next step in management?
(A) Bilateral neck dissections and surgical mediastinal exploration
(B) Bone marrow transplant
(c) Radiation therapy to the affected areas
(D) Staging laparotomy
(E) Systemic chemotherapy

Answers: 1.A, 2.C, 3.A, 4.E

Thank you

If you have any question please contact with us at:
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