MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE

UZHHOROD NATIONAL UNIVERSITY

DEPARTMENT OF ONCOLOGY

Lymphoma

Methodical instructions for 5, 6-year medical students' individual training

Uzhhorod – 2023

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Methodological guidelines approved:

Meeting at State University Department of Oncology

"Uzhhorod National University" protocol № 6 dated 20/01/2023.

at a meeting of the Academic Council of the Medical Faculty State University "Uzhhorod National University" record number 1 dated 16/02/2023.

Lymphomas

I. Topic actuality:

Malignancies of the lymphoproliferative system can be broadly classified into Hodgkin's lymphoma and all other lymphomas, which are termed the non-Hodgkin's lymphomas. The classification of these is complex and many different systems have been described of which the WHO REAL classified in To tumors of the immune system include Hodgkin's disease (Hodgkin's disease) and lymphocytic (non-Hodgkin) lymphoma. Lymphoma develop in the lymph nodes or lymphatic tissue parenhymatoznyh bodies. Lymphogranulomatosis occurs with a frequency of 3-4 cases per 100 000 population per year. Men suffer more (60-70% of cases). The average age of patients with Hodgkin's disease - 32 years, in other forms of lymphoma - 42 years.

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of malignancies of the lymphoid system. This heterogeneity (>30 entities) stems from the functions of the lymphoid arm of the immune system, which employs various types of lymphocytes that defend the organism from external (infectious) and internal (neoplastic) threats. Malignant lymphoid cells retain many qualities of their normal counterparts (B cells to produce immunoglobulins; T cells to travel to extra nodal sites such as skin and CNS). In some instances, the boundaries between leukaemia's and lymphomas become blurred, such as in ALL and acute lymphoblastic lymphoma, and CLL and small lymphocytic lymphoma, depending on the relative presence of a solid phase (lymphoma) versus circulating phase (leukaemia).

That is why we need to acquaint with work organization and equipment of department of radial therapy in radiological department of regional oncological clinic. It is very important to know the physical and technological bases of radiotherapy, principle of work and building apparatus for radial therapy.

II. Teaching aim:

2.1. The student must know:

Epidemiology, aetiology and risk factors of lymphomas' developing, their classification, clinical presentation, modern methods of diagnosis and treatment.

2.2. The student should be able to:

Put clinical diagnosis, stage of disease, make a plan of examination and algorithm of treatment, differential diagnosis of different lymphadenopathies.

Assess prognosis of patient, prescribe follow-up and monitoring of patient.

III. Basic level of knowledge and skills:

- classification and presentation of benign and malignant tumors.
- Structure and function of lymph nodes in normal and pathological cases
- methods of diagnosis and workup of lymphadenopathy.

IV. The program of self-preparation of the students:

№	Task Maintenance	Task maintenance concrete definition
1.	Collecting history	• Risk factors and family history of suspected lymphomas. • Epidemiology. • Classification. • Common complains and presentation.
2	Work-up and treatment plan	• Physical examination. • Biopsy, molecular types of lymphomas. • Primary imaging methods, modern methods of investigations. • Differential diagnosis of lymphomas, metastatic work-up. • Staging of lymphomas • Treatment of different stages of lymphomas.

V. Short methodical instructions for practical study work.

The duration of practical classes is 2 academic hours. Classes are held in oncological clinic and consist of four structural parts: learning the theoretical part of the topic; demonstration of thematic patient; students' work on practical skills under the supervision of a teacher; solving of situation tasks and test control learning.

- After introductory teacher's word, control of the level of knowledge and skills of the students.
- The group carried out the individual educational tasks.
- Students conduct curation of patients in the chemotherapy department.

VI. Content of the topic

Malignancies of the lymphoproliferative system can be broadly classified into Hodgkin's lymphoma and all other lymphomas, which are termed the non-Hodgkin's lymphomas. The classification of these is complex and many different systems have been described of which the WHO REAL classify

Hodgkin's lymphoma

Epidemiology

The crude incidence of Hodgkin's lymphoma (HL) in the European Union is 2.3 and the mortality is 0.4 cases/100 000/ year. Young adults aged 20–40 years are most often affected; however, a second incidence peak is seen in individuals aged 55 and older. Slightly more men than women are diagnosed with HL. Histologically, classical HL (cHL) accounting for ~95% of all HL cases is distinguished from nodular lymphocyte predominant HL (NLPHL) representing ~5% of all HL cases.

There is a bimodal age distribution, the two peaks of incidence occurring in young people aged 20–30 years and in later life over 70 years. Overall it is almost twice as common in men as it is in women

It is rare in the Japanese and in the US black population, and particularly high in the Jewish populations of the US and the UK.

Etiology

There is no proven aetiological agent responsible for the development of HL. Nodular sclerosing Hodgkin's is more common in more affluent households and the reverse is seen for other subtypes, which are more common in less affluent households. There is a strong association with infection with Epstein–Barr virus (EBV); EBV-associated Hodgkin's seems particularly prevalent in those under 10 years and over 60 years and in this group viral DNA can be identified in the cells in up to 50 per cent.

Risk factors

- Epstein- Barr virus in 50% cases- more in MC HD (60- 70%) than NS HL (15-30%) (Incidence is about 2.55 times higher)
- 100% of HIV associated HL are EBV (HIV infection is associated with higher incidence of HL, but HL is not a AIDS defining neoplasm)
- First degree relatives have fivefold increase in risk for HL
- High socio-economic status.

- Prolonged uses of human growth hormone.

Classification

Table 1: histological classification of HL

Name	Description	Prognosis
Nodular sclerosing HL	Characterized by collagen bands and lacunar variants of RS cells; the presence of one or more sclerotic bands is the defining feature. These bands usually radiate from a thickened lymph node capsule, often following the course of a penetrating artery, and are composed of mature, laminated, relatively acellular collagen. The sclerotic bands are birefringent in polarized light. In most cases, several broad collagenous bands can be identified, or fibrosis can be so extensive that isolated nodules of lymphoid tissue remain. The collagenous bands of nodular sclerosis enclose nodules of lymphoid tissue containing variable numbers of HCs and reactive infiltrates. Lacunar cells are a common type of RS cell present and may be found in large numbers or in sheets. They tend to aggregate at the center of nodules, sometimes forming a rim around central areas of necrosis. Diagnostic RS cells are present in variable numbers and may be difficult to identify in small biopsy specimens. Eosinophils, histiocytes, and sometimes even neutrophils are often numerous; plasma cells are usually less conspicuous.	good
Mixed-cellularity subtype	This intermediate subtype falls between lymphocyte-rich classical HL and lymphocyte-depleted classical HL. The capsule is usually intact and of normal thickness. A vague nodularity may be present at low magnification, but the presence of any definite fibrous bands would warrant classification as nodular sclerosis rather than mixed cellularity. At high magnification, a heterogeneous mixture of HCs, small lymphocytes, eosinophils, neutrophils, epithelioid and no epithelioid, histiocytes, plasma cells, and fibroblasts are present. Diagnostic RS cells and mononuclear variants are usually easy to find. Small foci of necrosis may be present, but the extent is much less than that seen in nodular sclerosis	moderate
Lymphocy	Many cases of lymphocyte-rich classical HL have a resemblance to	Good

te-rich	mixed cellularity HL, with vaguely nodular and less often diffuse pattern at low magnification. Hodgkin and RS cells are relatively rare and the background is dominated by small mature lymphocytes. Eosinophils and neutrophils are usually absent and if present are scanty and usually within the interfollicular areas. RS cells and variants are not easy to find but when encountered have identical features to the HCs of mixed cellularity. Some cases of lymphocyte-rich HCs may show a distinctly nodular appearance that may closely mimic nodular lymphocyte predominance HL and often contain relatively small germinal centers, with Hodgkin and RS cells present in and near the mantle zone, a pattern that has been called follicular HL.	
Lymphocyte depleted	Lymphocyte-depleted HL encompasses two variants: Diffuse fibrosis, and reticular. The most characteristic features are a marked degree of reticulin fibrosis surrounding single cells along with lymphocyte depletion. In contrast to nodular sclerosis, this subtype is not characterized by the presence of thick fibrous bands and the fibrosis envelops individual cells, not nodules of cells. HCs are usually easily identified, but increased numbers of HCs are not essential to the diagnosis. In the reticular variant, sheets of HCs, often showing pleomorphic features, are found.	Poor
Unspecified	This is a B-cell neoplasm with a nodular or nodular and diffuse proliferation of scattered large neoplastic cells termed “popcorn” cells (formerly called L&H cells, for lymphocytic and/or histiocytic RS cell variants). These large cells resemble Centro-blasts but are larger and have folded or multilobulated nuclei and multiple small basophilic nucleoli are often present adjacent to the nuclear membrane. The cytoplasm is broad and only slightly basophilic. These large cells are present within spherical nodules with numerous dendritic cells, histiocytes, and small lymphocytes. Ultrastructural studies demonstrate that popcorn cells have the appearance of Centro-blasts of germinal center. Epithelioid histiocytes are preferentially found in the outer rim of nodules. They are arranged in small groups or clusters and well-formed granulomas may be present in rare cases. Eosinophils and	Poor

	neutrophils are rare. Plasma cells are not common and are seen only between follicles. In diffuse areas, the popcorn cells are still often arranged in a vaguely nodular pattern. Classic Hodgkin and RS cells are completely lacking or are few in number. In some cases, popcorn cells may resemble lacunar cells because both cell types show irregularly shaped or lobulated nuclei, small nucleoli and broad pale to slight basophilic cytoplasm. The popcorn cells are often surrounded by rosettes of CD31, CD571 T-lymphocytes.	

Natural history

Typically, stepwise involvement of adjacent node groups occurs. The most common nodes involved are those in the neck. In this situation spread is to adjacent nodes in the supraclavicular fossa, the axillae and the mediastinum before involving para-aortic nodes below the diaphragm. Extra nodal involvement as a sole manifestation is rare and usually occurs in the context of extensive or bulky node disease.

Symptoms

Typically, the patient is aware of a painless enlarged node in the neck. This might have been present for many weeks or months but can develop more rapidly.

'B' symptoms are characteristic of lymphomas and are:

■ fever >38°C often with typical remittent pattern (Pel–Ebstein fever)

■ weight loss of >10 per cent body weight

■ night sweats (that include profound sweating, sufficient to drench bedclothes).

These constitutional symptoms are prognostically important.

Other uncommon but characteristic symptoms include generalized and often intractable itching and alcohol-induced pain in the enlarged nodes. Although the lymph nodes themselves are usually painless there might be some backache from para-aortic nodes and left sided abdominal pain from splenic enlargement.

Atypical presentations

- Unexplained itching.
- cutaneous disorders such as erythema nodosum.
- paraneoplastic cerebellar degeneration.
- nephrotic syndrome.
- immune hemolytic anemia & thrombocytopenia, hypercalcemia.

- pain in lymph node region on alcohol ingestion (is specific for HL but is seen in less than 10% of patients.
- back/bone pain is rare.

Differential diagnosis

The main differential diagnosis is between HL and non-Hodgkin's lymphoma. Other causes of lymphadenopathy will also be considered including infection, which can be either pyogenic, tuberculous or viral, e.g. EBV or CMV (cytomegalovirus), toxoplasmosis and other neoplastic conditions such as leukemia or carcinoma.

Diagnosis and investigations

Pathological diagnosis should be made according to the World Health Organization (WHO) classification from a sufficiently large surgical specimen or excisional lymph node biopsy to provide enough material for fresh frozen and formalin-fixed samples. In cHL, the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining while the detection of lymphocyte predominant (LP) cells is required for the diagnosis of NLPHL.

Physical examination: palpable painless lymphadenopathy, rubbery consistency

- cervical (60-80%), axillae (6-20%), inguinal (6-20%).
- Waldeyer's ring or occipital/epitrochlear lymphadenopathy rare.
- Splenomegaly, hepatomegaly, SVC syndrome due to mediastinal lymphadenopathy, CNS symptoms (multi focal leukoencephalopathy)

BIOCHEMICAL:

ESR- elevated level - poor prognosis,

LDH- correlate with bulk of disease,

CBC- anemia of chronic disease, lymphopenia, neutrophilia, eosinophilia.

Serum creatinine – for nephrotic syndrome,

ALP- liver/bone marrow involvement,

elevated serum calcium and sodium, hypoglycemia (due to presence of insulin auto antibodies)

HIV test: as anti-retroviral therapy can improve outcome in positive pations.

- Staging laparotomies (biopsy of liver, splenectomy & biopsy from multiple lymph nodes i.e. para aortic, mesenteric, portal & splenic hilar region if enlarged) were once popular for most patients with HL but are now done rarely because of an increased reliance on systemic rather than local therapy. The procedure can be helpful in rare cases where radio therapy is considered as sole t/t of early stage HL.

- Chest X-ray can show widened mediastinal shadow owing to enlarged nodes or, more rarely, lung parenchymal infiltration. Pleural effusion is also a recognized finding.
- CT and MRI CT scan of the chest, abdomen and pelvis will give the most accurate assessment of internal lymphadenopathy and has now superseded the use of bipedal lymphangiography as the imaging of choice for staging in lymphoma.

Additional staging information can be seen on fluorodeoxyglucose PET scans with normal size nodes demonstrating increased uptake indicative of lymphoma. PET can also have an important role in response assessment and follow-up.

Biopsy

A tissue diagnosis is mandatory to confirm the diagnosis and define the histological subtype of HL. This will usually take the form of an open lymph node biopsy where there is an accessible node in the neck, axilla, supraclavicular fossa or groin. Mediastinoscopy or laparoscopy could be required where there are no other sites accessible for biopsy.

Staging

The staging of HL follows the Ann Arbor classification:

■ Stage 1 – Involved lymph nodes limited to one node area only

■ Stage 2 – Involved lymph nodes involving two or more adjacent areas but remaining on one side of the diaphragm only

■ Stage 3 – Involved lymph nodes on both sides of the diaphragm

■ Stage 4 – Involvement of extra nodal organs denoted by the following suffixes:

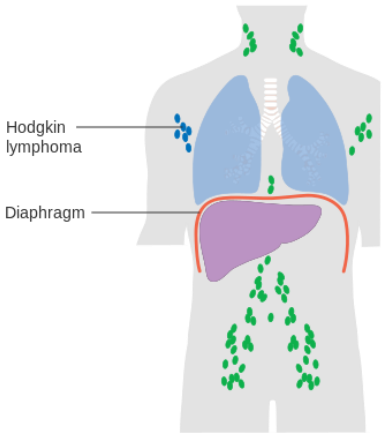
M – bone marrow

D – skin

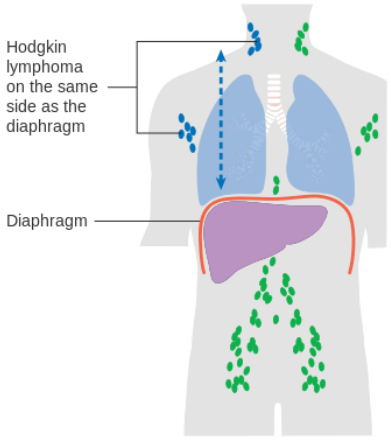
H – liver

S – spleen.

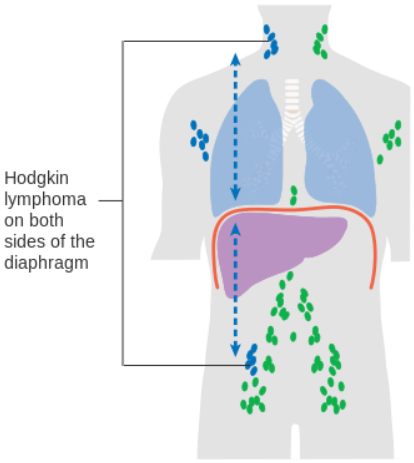
Each stage is further subclassified ‘A or ‘B’ according to the absence or presence, respectively, of B symptoms.



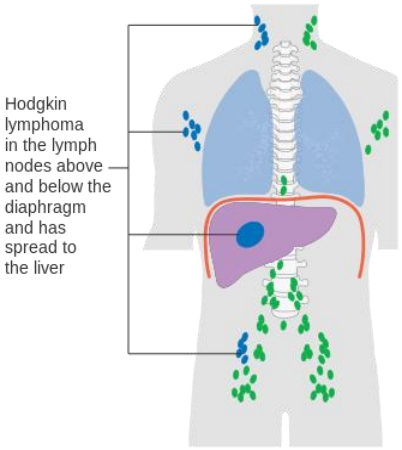
Stage 1 Hodgkin's lymphoma



Stage 2 Hodgkin's lymphoma



Stage 3 Hodgkin's lymphoma



Stage 4 Hodgkin's lymphoma

Treatment

- Early-stage (stage I to stage II) HL

Specific risk factors for unfavorable prognosis include: the presence of 3 or more involved lymph node areas, elevated ESR, bulky mediastinal mass and extra nodal disease. The preferred treatment for early-stage disease is combined-modality therapy consisting of combination chemotherapy (typically ABVD [doxorubicin, bleomycin, vinblastine, dacarbazine]) followed by involved-field radiotherapy.

Favorable disease is treated with 2 cycles of ABVD followed by 20 Gy radiation while unfavorable disease is typically treated with 4 cycles of ABVD followed by 30 Gy radiation.

Intensive chemotherapy with 2 cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) followed by 2 cycles of ABVD and radiotherapy improves tumor control in high-risk patients at the cost of higher toxicity.

- Advanced (stage III to stage IV) HL

The goal of therapy is cure. Initial treatment should be combination chemotherapy. Acceptable regimens include ABVD or escalated BEACOPP. Stanford V chemotherapy (doxorubicin, vinblastine, chlormethine, vincristine, bleomycin, etoposide, prednisolone) can be considered. The role of consolidation radiotherapy in advanced HL is controversial but generally recommended for patients with bulky disease (>5 cm), or for patients receiving Stanford V, in which radiotherapy is an essential component.

The acute side effects of therapy depend on the region treated and the dose employed. Most patients treated to the mediastinum develop esophagitis, clinically apparent as odynophagia that sometimes requires narcotic analgesics to maintain oral intake. Infra-diaphragmatic radiotherapy can cause nausea and/or diarrhea. Fatigue is common in all patients receiving radiotherapy.

- Refractory and relapsed disease

Management of relapsed HL must be individualized. The goal of therapy, at least initially, remains curative. The recommended treatment will vary and depends on several factors including previous first-line treatment (radiotherapy alone, chemotherapy alone, or combined-modality therapy), patient age and medical comorbidities, duration of first remission, and stage at relapse.

Role of surgery in HL

Rare instances in which surgery may be used to address Hodgkin lymphoma include:

- During diagnosis – When diagnosing lymphoma, it's typically ideal to examine an entire lymph node for signs of cancer. Surgeons may recommend removing one or more lymph nodes through an open excisional biopsy.
- During staging – To determine if a patient's lymphoma is confined to one specific area or if it has spread throughout the body, surgeons may perform a procedure known as a staging laparotomy.
- When treating symptoms such as pain, weakness and appetite loss – A splenectomy may be recommended for patients who are experiencing a reduced quality of life due to Hodgkin lymphoma side effects. This procedure may also be helpful for managing a platelet, iron or white blood cell deficiency following Hodgkin lymphoma treatment.

Monitoring, follow-up

During chemotherapy and radiotherapy monitoring, basic blood tests and imaging should be done at baseline and monitored during therapy. FBC with differential is monitored to assess treatment-induced bone marrow suppression. Metabolic panel and ESR are included as clinically indicated. TFT should be done as baseline and annually after treatment if the patient received radiotherapy to the neck. CXR and CT scan are done at baseline and as clinically indicated during therapy thereafter.

It is recommended that patients be followed every 3 months for the first 2 years after treatment, every 6 months for the next 3 years, and annually thereafter. Routine blood work and imaging are not necessary unless patients have concerning symptoms or abnormalities on examination. Thyroid studies should be obtained annually on patients who have received radiotherapy to the neck, given the high incidence of hypothyroidism in this population.

For women who have received radiotherapy to the chest or neck, breast cancer screening should be initiated 5 to 10 years after treatment or at 40 years of age, whichever occurs first.

Prognosis

The long-term prognosis for patients with early favorable HL is excellent with long-term disease control of 85% to 90% after brief chemotherapy followed by low-dose involved-field radiotherapy.

The most consistent adverse prognostic factor in early-stage HL is bulky mediastinal adenopathy, which was defined by the Cotswold's modification of the Ann Arbor staging system as a mediastinal mass exceeding one third of the intra-thoracic measurement at the T5-T6 inter-space. Other risk factors include advanced age, B symptoms, number of nodal sites, and histological sub-type. Seven important prognostic factors have been identified, which now comprise the International Prognostic Index. These are:

■ age >45 years

■ male

■ stage IV disease

■ haemoglobin <10.5 g/dL

■ total white cell count >16 □□109/L

■ lymphocyte count <0.6 □□109/L

■ serum albumin <40 g/L.

UNFAVORABLE FACTORS IN EARLY STAGE HL

- Bulky disease: defined as mediastinal mass >1/3 of intra thoracic diameter on CXRAY or >35% of thoracic diameter at vertebral level T5-6 or >10 cm in diameter on CT scan.

- ESR ≥ 50 if pt. is otherwise asymptomatic.
- > 3 sites of HL involvement.
- The presence B symptoms.
- The presence of extra nodal disease.

Advanced HL is a heterogeneous disease. Overall, the long-term disease control after chemotherapy alone or combined-modality therapy is approximately 60% to 80%. A prognostic scoring system has been developed in which 7 adverse factors with independent prognostic value (low albumin level, low hemoglobin level, leukocytosis, lymphocytopenia, male sex, older age, stage IV disease) can be used to predict freedom from progression. With no risk factors, the 5-year freedom from progression is 84% versus 42% for patients with 5 or more risk factors.

Hodgkin's lymphoma and COVID-19

Patients with Hodgkin lymphoma, their families, and caregivers should be vaccinated against SARS-CoV-2. Specific to SARS-CoV-2, data regarding the safety and efficacy of vaccines in immunocompromised patients are evolving, but there do not appear to be risks specific to this population. We recommend that patients with Hodgkin lymphoma receive a complete primary series of SARS-CoV-2 vaccine consisting of three vaccinations if an mRNA vaccine, followed by a fourth dose three months later despite the fact that they may not mount a robust immune response. Prophylaxis with long-acting antibodies were available provide an additional level of protection for patients undergoing chemotherapy. For more information about immunocompromised patients and SARS-CoV-2 vaccines, prophylaxis, and treatment. (American society of haematology).

NON-HODGKIN'S LYMPHOMA (NHL)

Epidemiology

NHL had been increasing in incidence by about 4% per year from the 1970s to 1998. The incidence has stabilized since 1998, possibly because the incidence of AIDS-related lymphomas among males has decreased. (National Cancer Institute: Surveillance Epidemiology)

Incidence of important NHL subtypes:

Diffuse large B-cell-lymphoma : 31%

follicular lymphoma: 22%

mantle cell lymphoma: 6%

marginal zone lymphoma: 5%

systemic anaplastic large T-cell lymphoma: 2%

Burkitt's and Burkitt-like lymphoma: 1%

primary CNS lymphoma: <1%

primary effusion lymphoma/body cavity lymphoma: <1%

angioimmunoblastic T-cell lymphoma: <1%.

Each year in the UK there are around 10 000 cases of NHL, 5300 cases in men and 4800 cases in women, making it the sixth commonest form of cancer, accounting for a total of 4500 deaths per annum. It occurs equally in men and women and the incidence increases with age, being relatively unusual under the age of 50 with 70 per cent of cases diagnosed over the age of 60 years. As with Hodgkin's lymphoma there is a marked low incidence in the Japanese and the US black population.

In the UK there are just over 4500 deaths each year and 10 500 patients presenting with this condition. There have been many descriptions of the pathological classification of this disease. Rather than achieving clarity, however, most have tended to confuse the situation further because of their complexity. In terms of clinical practice, the most significant divisions are into high - and low – grade lymphoma.
High - grade lymphoma is much more common than low - grade lymphoma. About 1000 people with low - grade lymphoma present each year. Slightly more men are affected than women. Lymphomas arise from lymphoid organs or lymphatic tissue associated with other systems that contain lymphatic tissue. The latter, the so-called 'extra nodal lymphomas', constitute up to 30% of all non-Hodgkin' s lymphoma.

Etiology

NHL has been associated with viruses and bacteria.
EBV with Burkitt's lymphoma.
EBV with AIDS-related primary CNS lymphoma.
EBV with nasal NK/T-cell lymphoma.
Hepatitis C virus (HCV) with splenic marginal zone lymphoma.
HCV with diffuse large B-cell lymphoma.
Human T-cell lymphotrophic virus type 1 with T-cell lymphoma.
Human herpesvirus 8 with primary effusion/body cavity lymphoma in HIV patients.
Helicobacter pylori with gastric mucosa-associated lymphoid tissue (MALT).
Borrelia burgdorferi with MALT lymphoma (cutaneous type).
Coxiella burnetii with B-cell non-Hodgkin's lymphoma.

NHL is a disease of the immune system and as such it has been linked to autoimmune disorders such as Sjogren's syndrome, rheumatoid arthritis, SLE, and coeliac disease.

NHL has been associated with both acquired immunodeficiency states, such as post-organ transplant and common variable immunodeficiency, and inherited immunodeficiency diseases, such as Wiskott-Aldrich syndrome, ataxia-telangiectasia, Chediak-Higashi syndrome, and Klinefelter's syndrome.

Several environmental factors, such as pesticides and phenoxyherbicides, have been mentioned in the literature as linked to NHL in farmers.

Table 2: International classification of NHL - WHO-REAL (Revised European American Lymphoma classification)

B-cell neoplasms	**T-cell neoplasms**
I – Precursor B-cell neoplasm – Precursor B-lymphoblastic leukaemia/lymphoma II – Peripheral B-cell neoplasms 1. Small lymphocytic lymphoma/chronic lymphocytic lymphoma 2. Lymphoplasmacytic lymphoma 3. Mantle cell lymphoma 4. Follicular lymphoma 5. Splenic marginal zone lymphoma 6. Hairy cell leukaemia 7. Plasma cell myeloma 8. Diffuse large B-cell lymphoma 9. Burkitt's lymphoma	I – Precursor T-cell neoplasm – Precursor T lymphoblastic lymphoma/leukemia II – Peripheral T-cell and NK-cell neoplasms 1. T-cell CLL/prolymphocytic leukemia 2. Large granular lymphocytic leukaemia 3. Mycosis fungoides/Sezary syndrome 4. Peripheral T-cell lymphomas, unspecified 5. Angioimmunoblastic T-cell lymphoma 6. Angiocentric lymphoma 7. Intestinal T-cell lymphoma 8. Adult T-cell lymphoma/leukaemia 9. Anaplastic large cell lymphoma
Indolent (low-grade): ■ Follicular lymphoma with any of the following cell types: – small cleaved cells – mixed small and large cleaved cells ■ Well-differentiated diffuse small cell lymphocytic lymphoma	**Aggressive (intermediate/high-grade):** ■ Follicular lymphoma containing predominantly large cells (Grade 3) – Diffuse lymphoma containing any of the following types: – small cleaved cells – mixed small and large cells – predominantly large cells ■ Immunoblastic ■ Peripheral T-cell lymphoma
Rarer types: requiring different management ■ Lymphoblastic; aggressive requiring leukaemia-type treatment ■ Small non-cleaved cell as in Burkitt's lymphoma: poorly responsive to standard chemotherapy requiring more intensive schedules ■ Mycosis fungoides: skin lymphoma having long natural history ■ MALTomas, arising in mucosal surfaces, usually low grade. In stomach respond to anti-*Helicobacter* therapy	

Natural history

Indolent low-grade lymphoma can remain asymptomatic for many years and, in the elderly, have little impact upon their life expectancy.

A high-grade immunoblastic or lymphoblastic lymphoma is an aggressive often rapidly fatal condition. Extranodal lymphoma can have a relatively benign course as in a low-grade skin lymphoma, existing as purplish nodules requiring little other than gentle local treatment from time to time. In contrast it can follow an aggressive course as in a high-grade lymphoma of the bowel or central nervous system.

In general, NHL, unlike Hodgkin's lymphoma, does not have a clear pattern of contiguous spread from one area to the next. Dissemination is often wide and unpredictable following a pattern closer to that of a carcinoma with relatively frequent hepatic and lung involvement.

Richter's syndrome refers to the transformation from a low-grade to a high-grade lymphoma, which can occur in up to 15 per cent of patients presenting initially with low-grade lymphoma. For this reason, re-biopsy of recurrent disease, particularly where there has been a period free from detectable disease or a change in growth rate is observed, should be considered before treatment

Symptoms

NHL usually presents with a painless lump in a lymph node area, most commonly the neck but also the axilla or groin. There can be backache owing to enlarged para-aortic nodes or upper abdominal pain from hepatosplenomegaly. 'B' symptoms as described for Hodgkin's are also an important feature, namely weight loss, fever and night sweats.

Other symptoms relate to the site of origin of an extra nodal lymphoma. NHL arising in Waldeyer's ring therefore will cause local symptoms similar to those of a carcinoma in these regions, with local pain or discomfort, and epistaxis or nasal discharge where the nasopharynx is involved. Gastrointestinal lymphoma usually presents with an acute abdominal event owing to haemorrhage, perforation or obstruction.

CNS lymphoma can cause symptoms of raised intracranial pressure with headache, vomiting and fits. Focal neurological features can cause bulbar palsy, diplopia, limb weakness and altered sensation.

Skin lymphoma usually presents as asymptomatic lumps but mycosis fungoides has a characteristic pretumor phase often lasting many years with chronic skin change, which can be itchy and resemble dermatitis in its clinical picture.

Signs

Enlarged lymph nodes will be palpable, typically painless, firm, 'rubbery' nodes clinically indistinguishable from those of Hodgkin's lymphoma but different from the hard-craggy nodes of carcinoma.

At extra nodal sites lymphoma often has a characteristic purplish appearance, stretching overlying surfaces and ulcerating only rarely. Hepatosplenomegaly is a common finding in both nodal and extra nodal lymphoma.

Investigations

Biopsy

A tissue diagnosis is mandatory to confirm the diagnosis and define the histological subtype of NHL. This will usually take the form of an open lymph node biopsy where there is an accessible node in the neck, axilla, supraclavicular fossa or groin. Mediastinoscopy or laparoscopy could be required where there are no other sites accessible for biopsy.

Blood count

A full blood count can show signs of mild anaemia or pancytopenia if there is bone marrow involvement. A high white cell count composed predominantly of lymphocytes can also be found and is a relatively poor prognostic sign.

ESR

The ESR will be raised; an ESR >40 mm/h is a further poor prognostic feature.

Biochemistry

The serum lactate dehydrogenase (LDH) is a marker of disease activity. Routine biochemistry can show signs of hepatic infiltration. Renal failure is an occasional complication of massive para-aortic node enlargement causing ureteric obstruction. Hypercalcaemia is associated with HTLV-associated lymphomas.

Radiography

The chest X-ray might show mediastinal or hilar lymphadenopathy; more rarely infiltration of the lung parenchyma, pleural nodules or a pleural effusion will be found.

CT scan

Imaging of the abdominal and pelvic lymph nodes

A CT scan of the brain will be performed for CNS lymphoma, which can be further supplemented by an MRI scan to image potential spinal disease.

PET CT

PET can give additional information showing evidence of active disease in normal sized lymph nodes resulting in upstaging in relation to CT stage. It can also be useful in assessing response, a negative PET scan at completion of treatment having a high predictive power for long relapse-free survival.

Bone marrow examination

Bone marrow examination will be required in all cases to assess the possibility of marrow infiltration.

Additional staging information can be seen on fluorodeoxyglucose PET scans with normal size nodes demonstrating increased uptake indicative of lymphoma. PET can also have an important role in response assessment and follow-up.

Staging

The Ann Arbor staging system is used for NHL as for Hodgkin's lymphoma with the further addition of a suffix 'E' where the lymphoma has arisen in an extra nodal site. For example, an NHL arising in the tonsil with involved nodes in the neck would be stage 2 by virtue of the presence of two or more sites all on the same side of the diaphragm and be designated stage 2E, having arisen in an extra nodal site.

Treatment

- Indolent low-grade NHL

(Common types are follicular and diffuse small cell lymphoma in WHO-REAL classification.)
This is a condition that is rarely curable but usually has a long clinical course. Localized low-grade NHL (stage 1A) is treated using local radiotherapy. The involved area only is treated, using low doses of 20–30 Gy in 2–3 weeks.

The first-line chemotherapy of choice is RCVP comprising rituximab, cyclophosphamide, vincristine and prednisolone.

In elderly patients an alternative is to use single-agent oral chemotherapy, of which the most popular is chlorambucil or cyclophosphamide: 70–80 per cent of patients will enter remission with such treatment.

- Relapse

Low-grade lymphoma that is not localized is never cured, although survival for many years is to be expected. When relapse does occur, further chemotherapy will be given; second-line treatment can include fludarabine often in combination with Adriamycin or mitozantrone and dexamethasone (FAD or FMD), which appear more active than the single drugs alone. Retreatment with an alkylating agent such as chlorambucil or cyclophosphamide is often successful and local sites causing symptoms can be irradiated.

- Palliation

Steroids alone in moderate doses (40–60 mg of prednisolone) can have a valuable antitumor effect as well as conferring general effects such as improvement in appetite and general wellbeing.

Hemi-body irradiation is a valuable palliative treatment for widespread NHL no longer responsive to chemotherapy.

- Aggressive high-grade lymphoma

(Common type is a diffuse large cell lymphoma in WHO-REAL classification.)

This is a much more dangerous condition than low-grade lymphoma and in general requires more intensive therapy.

- Nodal lymphoma

Localized high-grade NHL (stage 1A and 2A) is treated with a short course of chemotherapy (typically three courses of RCHOP (rituximab, cyclophosphamide, Adriamycin, vincristine, prednisolone) followed by local irradiation to the involved sites delivering a dose of 30 Gy in 3 weeks.

Advanced disease (stage 1B, 2, 3 or 4) is treated with chemotherapy. As for Hodgkin's lymphoma, consideration should be given to sperm banking for young males and all patients should be well hydrated and started on allopurinol to prevent tumour lysis syndrome.

- Specific chemotherapy

Usually, combination chemotherapy is given of which the most widely used is RCHOP, rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisolone. The first four drugs are given intravenously on day 1 of a 21-day cycle with oral steroids on the first 5 days. A total of six to eight courses is usually given, the standard dictum being to deliver two courses of chemotherapy beyond complete clinical remission.

Prognosis

There are four major independent prognostic features in non-Hodgkin's lymphoma:

■ age

■ performance status

■ stage (3 or 4 worse than 1 or 2)

■ serum lactate dehydrogenase.

These have been validated and are referred to as the International Prognostic Index (IPI).

The overall prognosis for indolent low-grade lymphoma is better than that for intermediate or high-grade lymphomas, with median survivals of 8–10 years reported from most centres.

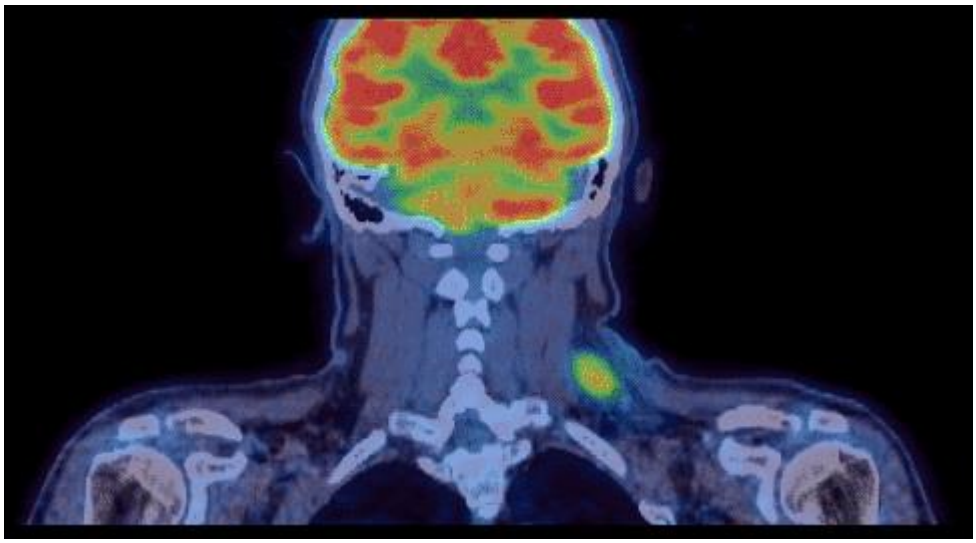
Early localized disease will be associated with high cure rates, over 90 per cent for indolent lymphoma and 85 per cent for aggressive forms following radiotherapy preceded in the latter by short-course chemotherapy Extra nodal lymphoma, even when localized, tends to have a worse prognosis than nodal lymphoma; Waldeyer's ring and skin do better than gastrointestinal tract, which does better than CNS. More advanced aggressive high-grade NHL will respond to chemotherapy in most patients with complete regression of disease in 70–80 per cent; however, long-term survival figures tend to fall below 50 per cent at 5 years from treatment.

VII. QUESTIONS FOR SELF-CONTROL:

1. Epidemiology and risk factors of Hodgkin's and non-Hodgkin's lymphomas.
2. Pathology of Hodgkin's lymphoma, modes of spreading.
3. Histological types of Hodgkin's and non-Hodgkin's lymphomas.
4. Clinical presentation, history, symptoms and signs.
5. Lymphoma staging, diagnostics, modern methods of investigations.
6. Differential diagnosis of lymphomas.
7. Principles of treatment of Hodgkin's lymphoma.
8. Principles of treatment of non-Hodgkin's lymphoma.
9. prognosis and follow-up.

VIII. Tasks for verification of concrete teaching aims achievement:

1- A 32-year-old woman presented with a lump on the left side of her neck. She was well with no weight loss, fevers or night sweats. A biopsy showed nodular sclerosing Hodgkin's disease. She had a staging CT-PET scan. The only FDG avid lymph node was in the left supraclavicular fossa (see image). What is the stage of her disease?



a- Stage IA
b- Stage IB
c- Stage IIA
d- Stage IIB
e- Stage IIIA

2- A 23-year-old female comes into the clinic for fevers and weight loss. She has lost 30 pounds in the past 2 months. She also has been waking up essentially every other night for the past two weeks soaked in sweat. She thought it was just her thermostat, but, after having changed she still soaked the sheets at night. She is secretary at a law firm. She has also noticed a bump under her armpit. Every Friday night the firm goes out for cocktails and she notices that the bump hurts only when she has had a bit too much, otherwise it is nontender. Physical exam revealed normal vitals, a BMI of 19, no cervical lymphadenopathy, no inguinal lymphadenopathy, but a single hard, fixed, firm, and nontender mass, 1cm*1.5 cm in the left axilla. Breast exam were clear of masses, and no history of breast cancer. What is the next best step in the management of this patient?

a- Excisional biopsy
b- Fine needle aspiration of the mass
c- Ultrasound of breast
d- Chest x ray
e- Mammogram

3- A 28-year-old male is seen for nontender lymph node. Excisional biopsy is undertaken which demonstrates CD15 and CD30 positive cells. The diagnosis of lymphoma is made. A CXR identified a single lymph node in the thorax. The CT scan revealed 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 3
b- Stage 4
c- Stage 1
d- Stage 2

4- A 19-year-old male comes to the clinic for a neck mass. There were no symptoms, it was firm, non-tender, and was not fixed in place, it was 2.5*2cm. an excisional biopsy is preformed and immunohistochemical staining showed scatter binucleate cells that are positive for CD15 and CD30. The lymph node architecture shows the replacement of normal tissue by mixed population of cells including histiocytes, lymphocytes, plasma cells, and eosinophils, Presence of multinucleated nucleus. What is the most likely diagnosis?

a- Hodgkin disease
b- Hairy cell leukemia
c- B-cell lymphoma
d- Waldenstrom macroglobulinemia
e- Burkitt's lymphoma

5- A 64-year-old male presents with cervical lymphadenopathy. He has been unable to wear a tie, cannot fasten the top button of his shirt, and is having trouble shaving. The bumps in his neck do not hurt. He has had night sweats for the past month, but has not weight loss or fevers. Physical exam revealed normal vitals. There is bilateral cervical lymphadenopathy and bilateral axillary lymphadenopathy. There is no inguinal involvement or organomegaly. Excisional biopsy of axillary node demonstrates follicular non-Hodgkin's lymphoma. A CT of the chest and abdomen shows 4 regions of lymphadenopathy in neck and chest, but no evidence of disease below diaphragm. Which if the following is the next step in management?

a- Cyclophosphamide, vincristine, and prednisone with rituximab
b- Bone narrow biopsy
c- Observation with follow up in 3 months
d- Doxorubicin, bleomycin, vinblastine, dacarbazine
e- Cyclophosphamide, vincristine, and prednisone with radiotherapy

6- A 27-year-old-female is being treated for Hodgkin's lymphoma. She is on her 9^{th} cycle of ABVD therapy. She has used dexamethasone for nausea control. As a part of her surveillance during chemo, a 2D echocardiogram is obtained that revealed decreased ejection fraction. Which of the following drugs most likely caused these symptoms?

a- Adriamycin.
b- Cyclophosphamide
c- Bleomycin
d- Cisplatin
e- Vincristine

7- A 15-year-old boy presents with a 2-month history of non-tender left axillary swelling. Ultrasound demonstrates an enlarged 3.1 cm short axis lymph node. On biopsy, a small number of Reed-Sternberg cells are seen. Which variant of this condition carries the best prognosis?

a- lymphocyte depleted
b- lymphocyte rich
c- mixed cellularity
d- nodular lymphocyte predominant
e- nodular sclerosing

8- Stage III B in Hodgkin's disease means:

a- Involvement of one group of lymph nodes, no intoxication symptoms.
b- Involvement of Pirogov-Valdeyyer ring, presence of symptoms of intoxication.
c- Involvement of lymph nodes on either side of the diaphragm, symptoms of intoxication.
d- Involvement of 2 or more groups of lymph nodes on the same side of the diaphragm, no symptoms of intoxication.

9- What histologic variant of Hodgkin's disease is most unfavorable?

a- Nodular sclerosis.
b- Mixed cellularity.
c- Lymphocyte rich (nodular type).
d- Lymphocyte rich (diffuse type).
e- Lymphocyte depleted.

10- Which group of lymph nodes are often increased in clinics of Hodgkin's disease?

a- Cervical.
b- Inguina.
c- Retroperitoneal.
d- Popliteal.
e- Mediastinal.

11- Which of the following is true of the pathology of Hodgkin’s lymphoma?

a- The cells stain with T-cell surface markers.

b- The presence of large binucleate cells is characteristic.

c- Extra nodal sites are frequently involved.

d- Splenic involvement is rare.

e- The lymphocyte-depleted subgroup has the best prognosis.

12- Which cytostatic agents are included in the ABVD regimen used to treat Hodgkin's disease?

a- doxorubicin + bleomycin + vinblastine + dacarbazine.

b- doxorubicin + bleomycin + cyclophosphamide.

c- cisplatin + cyclophosphamide + doxorubicin.

d- 5-fluorouracil + mitomycin C.

e- cyclophosphamide, vincristine, procarbazine.

13- Subgroup A of Hodgkin's disease means:

a- Symptoms of intoxication.

b- No symptoms of intoxication.

c- Swollen lymph nodes.

d- Enlargement of the spleen.

e- Lesion of the thymus gland.

Correct answers: 1-b, 2-a, 3-d, 4-a, 5-b, 6-a, 7-d, 8-c, 9-c, 10-a,11-b,12-a, 13-b.

Task 1

A 32-year-old man for 3 months notices a periodic rise in temperature up to 37.50C, sweating, more at night, itchy skin, dry cough, shortness of breath. Objectively: swelling of neck veins, neck thickening. General blood analysis: ER – 3.2 *1012/l, Hb – 155 g/l; CP – 1, platelets – 204 *109/l, L – 10.5 * 109/l: eosinophils – 4%, myelocytes – 1%, young – 3%, p – 7%, c – 63%, l – 16 %, m - 6%, ESR - 65 mm/h. A chest X-ray shows an expansion of the mediastinum, more in the upper half.

1. Preliminary diagnosis.

2. Additional examination methods needed by the patient. Which diagnostic procedure is mandatory for diagnosis?

3. Treatment tactics.

Task 2

a 26-year-old man, have enlarged cervical and axillary lymph node on the left were found on a professional examination. The nodes are mobile, densely elastic, painless, not joined together and by the surrounding tissues, the skin over them is not hyperemic. Patients do not complain. General blood analysis: ER – 3.5 *1012/l, Hb – 135 g/l; CP – 1, platelets – 300 *109/l, L – 10 * 109/l: eosinophils – 2%, young – 2%, p – 7%, c – 63%, l – 20%, m – 6%, ESR - 35 mm/h. A biopsy of the left axillary node was performed. Berezovsky-Sternberg cells were found in the biopsy.

1. Preliminary diagnosis.
2. Features of the impression of lymph nodes in this disease.
3. What complications can be expected with this disease.

IX. Suggested Literature:

IX 1. Basic:

1. NCCN clinical practice Guidelines of Hodgkin's lymphoma, February 2022.

2. Cancer principles and practice of oncology – DeVita, Hellman and Rosenberg's ,10th edition

3. ANNALS OF ONCOLOGY, ESMO Clinical Practice Guidelines of Hodgkin's lymphoma cancer treatment, 2019.

4. Surgical oncology, theory and multidisciplinary practice 2nd edition,2020.

5. Practical radiation oncology, 1st edition,2020.

IX 2. Additional:

1. Textbook of complex general surgical oncology -SHYNE Y. MORITA, CHARLES M. BALCH, V. SUZANNE KLIMBERG, TIMOTHY M. PAWLIK, MITCHELL C. POSNER, KENNETH K. TANABE, 2018.

2. Clinical oncology, basic principles and practice – Anthony J. Neal and Peter J. Hoskin ,4th edition.

3. American society of hematology.

4. manual of clinical oncology (Lippincott manual), 8th edition.

X. CONTENT