THE MINISTRY OF HEALTH, LABOUR AND SOCIAL PROTECTION OF REPUBLIC OF MOLDOVA

„NICOLAE TESTEMIȚANU" STATE UNIVERSITY OF MEDICINE AND PHARMACY

Buruiană Sanda

DIAGNOSIS AND CLINICAL FEATURES OF NON-HODGKIN'S LYMPHOMAS

(methodical guidelines for students)

CHIȘINĂU, 2020

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LIST OF ABBREVIATIONS

ALCL – Anaplastic large cell lymphoma
BCL – intracellular protein factor
CD – Claster of differentiation
CNS – central nervous system
DLBCL – Diffuse large B-cell lymphoma
EBV – Ebstein-Bar virus
ECOG – The Eastern Cooperative Oncolgy Group
FLIPI – International prognostic index follicular lymphoma
HHV – human herpes virusul
HLA-DR – Human leukocyte antigen
HTLV – human T lymphotropic virus
Ig – immunoglobulin
IPI – International prognostic index
LDH – Lactate dehydrogenase
MALT – Mucosa associated lymphoid tissue
MYC – proto-oncogene
NK – natural killer
SLE – Systemic Lupus Erythematosus
WHO – Word Health Organisation

NON-HODKIN'S LIMPHOMAS

Definition

Non-Hodgkin's lymphomas (NHL) exhibit a heterogeneous group of malignancies within lymphatic tissue. They are not homogeneous according to the morphological, immunohistochemical, cytogenetic, clinical and hematological structure, response to treatment and prognosis.

Preface

These methodical guidelines include the basic topics necessary for the student to make the diagnosis of non-Hodgkin's lymphoma (NHL) and to develop treatment principles. The methodical guidelines are an attempt to make accessible the subject matter about NHL necessary for the students to be comprehended. The major objective is to support the students of the faculties of Medicine and Preventive Medicine. There have been defined notions, which will contribute to the enrichment of the knowledge in the field and will be useful in the stages of knowledge assessment. Particular attention will be paid to the clinical activity of the student at the patient's bed, when carrying out practical maneuvers, tests and situational problems on the given subject. In order to gain a better understanding of the subject matter presented in this methodical guidlines, we endeavored to provide it with graphical material (tables, figures, diagrams), images, clinical cases, control tests.

Duration of the seminar

The seminar lasts 5 hours.

The aim of the seminar

Studying the epidemiology, etiology, pathogenesis, clinical manifestations, laboratory methods and medical equipment applied for the diagnosing NHL, mastery treatment principles.

Objectives of the seminar

1. Knowledge development on the etiology, epidemiology and pathogenesis of NHL;
2. Development of knowledge of the clinical, hematological, morphological and immunohistochemical features of NHL;
3. Acquiring practical skills in making the diagnosis of NHL;

4. Developing knowledge of the differential diagnosis of NHL;
5. Mastery general treatment principles of NHL.

The place of the seminar

1. In the Nicolae Testemițanu SUMPh Hematology Departement.
2. Hematology sections of the Hematological Department of the IMPH Oncological Institute of the Republic of Moldova.
3. Hematology offices in the Diagnostic Consulting Center of the IMPH Oncological Institute of the Republic of Moldova.

Methods and materials for the seminar

Teaching methods used

Teaching methods and procedures are used for effective learning and achievement of the proposed objectives, such as:

- presentation of the subject giving definitions, description, explanation, demonstration;
- collective discussion, problematization;
- summarizing.

Various forms of independent, frontal, group, interactive activity are used in the seminars.

Methods of evaluation

- questioning on the subject
- situation problem solving
- analysis of clinical cases
- doing single choice and multiple choice tests
- individual work
- assessment of practical skills
- Taking exam

Materials for the seminar

Teaching materials such as tables, schemes, algorithms, photographs, international guides are used for deeper learning of NHL. Power Point presentations are used at seminars as well.

Questions for self-training of the student

1. Etiology and epidemiology of non-Hodgkin's lymphomas.
2. Pathogenesis of non-Hodgkin's lymphomas.
3. Morphological classification of non-Hodgkin's lymphomas.

4. International clinical classification of non-Hodgkin's lymphomas.
5. Clinical features of non-Hodgkin's lymphomas.
6. Clinical picture of non-Hodgkin's lymphomas.
7. Diagnosis of non-Hodgkin's lymphomas.
8. Hematological changes in non-Hodgkin's lymphomas.
9. The importance of trepanobiopsy in non-Hodgkin's lymphomas.
10. Differential diagnosis of non-Hodgkin's lymphomas.
11. Treatment principles of non-Hodgkin's lymphomas.

Non-Hodgkin's lymphomas etiology

At present it is considered that there are multiple risk factors that can contribute to the appearance of NHL [1, 2, 3].

1. Ionizing radiation
2. Hereditary factors
3. Congenital immunodeficiency states
4. Acquired immunodeficiency states: changes secondary to prolonged immunosuppressive treatments, AIDS.
5. Primary or secondary autoimmune disorders (SLE, rheumatoid polyarthritis, Sjögren's syndrome),
6. Viruses: HIV, Epstein-Barr, HTLV-I, HHV-8, hepatitis C virus.
7. Other infectious agents such as Helicobacter pylori, chlamydia or chronic antigenic stimulation in different areas, especially in the lymphoid tissue associated with mucous membranes.
8. Chemical substances (organic solvents: organophosphorus insecticides, benzene, etc.).

Non-Hodgkin's lymphomas epidemiology

NHL is a pathology with an tendency to increase morbidity worldwide and at the same time in the Republic of Moldova. NHL morbidity in the Republic of Moldova is 4.1 per 100,000 population [4]. NHLs are some of the most common malignancies [5]. To date NHL remains one of the common causes of mortality in the world. According to the annual literature data, 450,000 new cases of the disease are recorded and 225,000 of them have been lethal. [6, 7]. The incidence of NHL is 15-20 per 100,000 population with an increase of 3-4% annually [3]. Being

monoclonal by origin, these tumors differ by morphological, immunohistochemical and cytogenetic picture, clinical evolution and response to treatment. NHL affects people of all ages, including children [4, 8, 9]. Morbidity increases with age, reaching a maximum of at the age over 60. The average age of affectation is 50 years [10]. In the local stages the survival of patients with complete remission at the age over 75 is 75-77% [11]. That is the reason why it is necessary to diagnose patients with NHL in the local stages (I and II).

Pathogenesis of non-Hodgkin's lymphomas

Lymphocytes develop from bone marrow stem cells, where B-lymphocytes undergo independent antigen-differentiation-pro-B-lymphocyte differentiation stage. At this stage CD19 appears on the cell membrane, which is a common marker for all B-lymphocytes. The occurrence of CD19 takes place in cells expressing HLA-DR molecules often in association with CD38, CD34, TdT [12]. CD10 [13] appears at the next stage of pre-B-lymphocyte differentiation on the lymphocyte membrane. Subsequently, CD20 appears on the membrane and the cell obtains the pre-B-lymphocyte immunophenotype. This stage corresponds to the stage of mature B-lymphocyte. The antigen-independent differrentiation process of B-lymphocytes ends with the expression of IgD, which coexists with IgM. The presence of IgM + IgD, CD19, CD20 on the membrane allows us to consider mature B-cell lymphocytes to be able to react with antigens and account for 60% of peripheral blood B lymphocytes [12, 14].

The mature B-lymphocytes leave the bone marrow, enter the bloodstream, reach the peripheral lymphatic organs (lymph nodes, spleen, liver, thymus, etc.), where the *antigen-dependent* differentiation stage occurs in contact with antigens.

In lymph nodes B-mature lymphocytes get in the primary follicles without germinal center. Secondary follicles differ from the primary ones by the presence of the germinal center.

The morphology of cells in the primary follicle corresponds to the small lymphocyte, most of them are without signs of activation. Lymphocytes express on the membrane of peripheral B cells phenotype: CD19, CD20, CD22, CD24, CD37.

CD23, CD5, CD10, CD38 activating antigens are commonly absent [13]. The CD5, CD23-B-lymphocyte antigens being activated migrate into the follicle, the structure of which changes after accelerated proliferation and appear in the germinal center and the so-called mantle area. Some of the cells migrate and form the marginal area, which surrounds the follicles and they remain there as "memory" B-cells. [12].

In the germinal center the process of antigen-dependent maturation and differentiation of B-cells takes place. In the germinal center, B-cells lose CD23 and transform into centroblasts which the expression CD77, CD10, CD19, CD20, CD38 is characteristic. Of a part of centroblasts are differentiated into centrocytes – small cells with a cleaved nucleus [12].

"Memory" B-cells are formed out of centrocytes - plasmocyte cells, which lose the majority of B-cell receptors with CD38- preservation, only. Mature plasmocyte cells exude immunoglobulins, which ensures the humoral function of the organism.

The marginal zone of the follicle cells of the lymph nodes is in small quantities compared to the spleen and lymphatic tissue of the mucous membranes. Their immunophenotype corresponds to the activated B-cells in the final stages of differentiation (CD19, CD20, CD22, CD37, CD40). The expression of CD21, CD23, CD24 is usually absent, that differs them from the cells of the germinal centers and the mantle area of the follicles. This type of cells more closely resembles lymphocytes from the marginal area of the spleen, but differs from them by the familiar expression of CD20, CD39, CD38 [15]. These data are shownin table 1.

Natural killers (NK-cells) exhibit the lymphocyte fraction lacking T- and B-cell markers. Their phenotype is CD3 +, CD16 +, CD56 +. Their content is higher in the liver and spleen, and they are found amounts in small numbers in the lymph nodes, bone marrow, lungs, lymph follicles of the small intestine. Morphologically they correspond to large granular lymphocytes [15].

Table 1

Stages of lymphocyte B differentiation

	B Lymphocytes	Ig Genes	Ig	CD	
Independent antigen	Stem Cell	Germ line	abs	CD34	Bone marrow
	Pro-B-lymphocyte	Germ line	abs	CD19, CD79a, CD34, BSAP, TdT	
	Pre-B-lymphocyte	IgH, bond-μ rearrangement	Ig μ	CD19, CD45R, CD79a, CD34, CD10,	
Dependent antigen	Immature B lymphocyte	IgL/IgH rearrangement	IgM	CD19, CD20, CD45R, CD79a, CD10, BSAP	Peripheral lymphatic organs
	Mature B lymphocyte	IgH/L rearrangement	IgM/IgD	CD19, CD20, CD45R, CD79a, CD5, BSAP	
	Germ cell lymphocyte	IgH/L rearrangement	Ig (min/abs)	CD19, CD20, CD45R, CD79a, CD10, BCL6	
	„Memory" B lymphocyte	IgH/L rearrangement	IgM	CD19, CD20, CD45R, CD79a, BSAP	
Differentiation	Plasmatic cell	IgH/L rearrangement	IgG>IgA>IgD	CD38, Vs38c, CD138	

Thus, the differentiated lymphocytes remain morphologically mature in the lymph nodes, spleen, intestinal submucosa and other organs until antigenic collisin. If the action of the antigen has taken place, then a new cycle of multiplication and differentiation of lymphocytes begins which again pass through the morphological stages of prolymphocytes, blast cells, immunoblasts. B-lymphocytes pass through the blast stage at least 3 times:

a) at the level of the stem cell class
b) at the primary immune response stage
c) at the secondary immune response stage when the "memory" cell turns into the immunoblast and finally - into plasmocyte.

At all these levels of cell differentiation, neoplasms can develop *(Fig. 1)*.

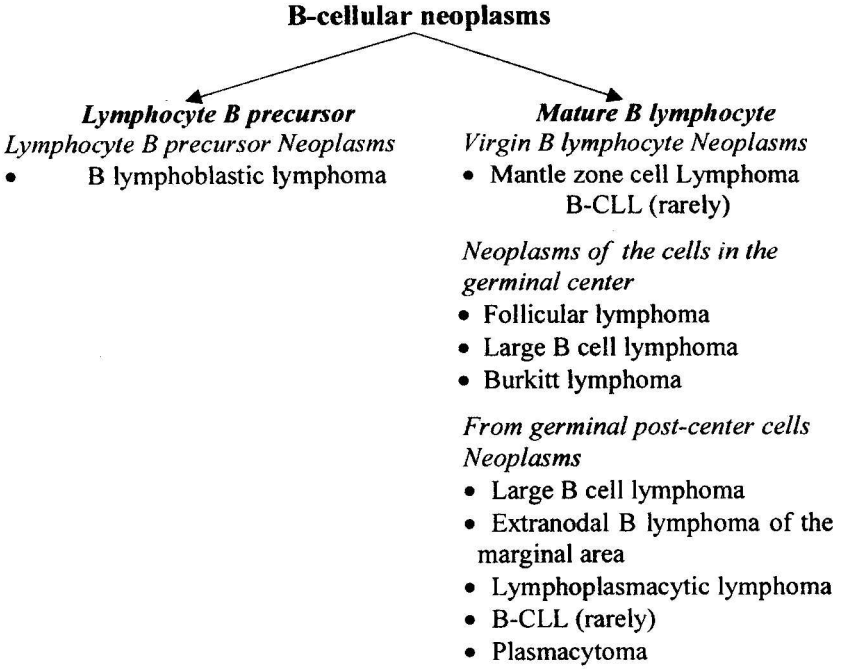


Fig. 1. Substrate of B cell neoplasms.

Morphological classification of non-Hodgkin's lymphomas

To make the diagnosis of NHL diagnosis, the morphological, immunophenotypic, chromosomal features are taken into account. These criteria were applied at the revision of the International Classification of the hematopoietic and lymphatic system neoplasms of the WHO in 2016 [16].

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma

Hairy cell leukemia variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia
Duodenal-type follicular lymphoma
Pediatric-type follicular lymphoma
Large B-cell lymphoma with IRF4 rearrangement
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type
Activated B-cell type
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV+ DLBCL, NOS
EBV+ mucocutaneous ulcer
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma

ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8+ DLBCL, NOS
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
High-grade B-cell lymphoma, NOS
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T and NK neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV+ T-cell lymphoma of childhood
Hydroa vacciniforme–like lymphoproliferative disorder
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Indolent T-cell lymphoproliferative disorder of the GI tract
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8+ T-cell lymphoma
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma

Follicular T-cell lymphoma
Nodal peripheral T-cell lymphoma with TFH phenotype
Anaplastic large-cell lymphoma, ALK+
Anaplastic large-cell lymphoma, ALK–

International clinical classification of non-Hodgkin's lymphomas

The stage of the disease is determined according to the International Clinical Classification developed in Ann Arbor (USA, 1971) [17, 18].

Stage I. Lesion of a single region of lymph nodes (I) or a single extranodal organ (I E).

Stage II. Lesion of two or more regions of lymph nodes on the same side of the diaphragm (II) or primary localized involvement of an extranodal organ and one or more regions of lymph nodes on the same side of the diaphragm (II E).

Stage III. Lesion of two or more regions of lymph nodes on both sides of the diaphragm (III) or primary localized involvement of an extranodal organ and two or more regions of lymph nodes on both sides of the diaphragm (III E).

Stage IV. Diffuse involvement of one or more organs or tissues with or without lymph nodes (*Fig. 2*).

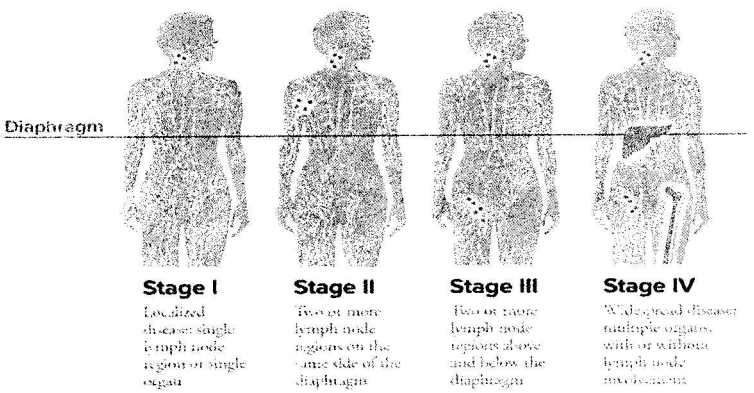


Fig. 2. Clinical stages of NHL.

Each clinical stage is subdivided according to the presence or absence of the symptoms of general intoxication:

A without symptoms of general intoxication

B with symptoms of general intoxication (*Fig. 3*).

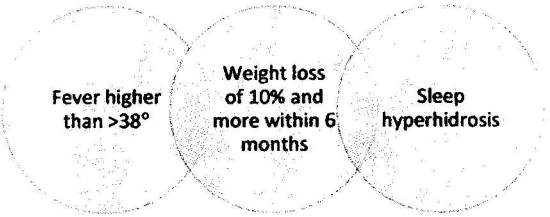


Fig. 3. Signs of general intoxication.

Depending on the presence of biological signs of activity of the pathological process, each stage is divided into a (absence of biological signs of activity) and b (presence of biological signs of activity of the tumor process):

a. ESR>30mm/hour
b. Hyperfibrinogenemia (>5.0 g/l)
c. Hyper α2 globulinemia (>10 g/l).
d. Ceruloplasmin (>0.4 Un)
e. Haptoglobin (>1.5 mg%).

The determination of the clinical stage (degree of spread) of the NHL is based on:

1. ***The clinical examination*** of the patient by palpation of all the groups of lymph nodes, liver, spleen, as well as the possible presence of symptoms B (fever above 38°, night sweats and weight loss);
2. ***laboratory investigations:*** hemolymphogram of peripheral blood, ESR, fibrinogen, LDH, α2 globulin, alkaline phosphatase, biochemical tests for renal and hepatic functions, serum uric acid;
3. ***imagistic investigations:*** chest X-ray, mediastinum tomography, nasopharyngeal tomography, completed with computerized tomography of the neck, chest, abdomen and pelvis; positron emission tomography (PET);
4. ***endoscopic investigations:*** fibroepipharyngoscopy, fibrogastroduodenoscopy and fibrocolonoscopy;

5. ***cytological investigation – myelogram (puncture of the bone marrow);***
6. ***histological investigation*** – bone marrow biopsy from the iliac bone (*fig. 4*).

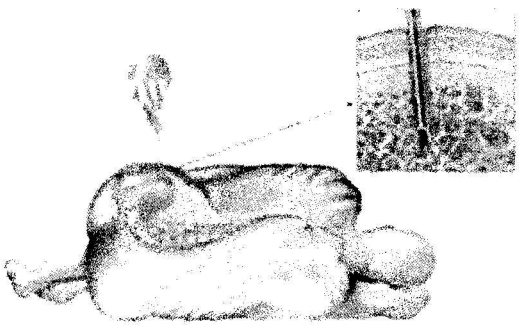


Fig. 4. Position of the patient during trepanobiopsy of the iliac bone.

Clinical features of non-Hodgkin's lymphomas

Depending on the aggressiveness of the NHL tumor process, they are divided into:

1. indolent variants (with low degree of malignancy)
2. aggressive variants (with a high degree of malignancy) [19].

Indolent NHLs include:

- small lymphocytic lymphoma
- marginal zone lymphoma
- grade I and II follicular lymphoma
- lymphoplasmacytic lymphoma.

Aggressive NHLs include:

- Grade III follicular lymphoma
- Diffuse large B cell lymphoma
- Mantle cell lymphoma
- Lymphoblastic lymphoma
- Immunoblastic lymphoma
- Anaplastic lymphoma
- Burkitt lymphoma etc.

Indolent NHL is characterized by slow progressive evolution, moderate reaction to chemotherapy and rarely definitive healing. In aggressive NHLs the evolution is rapid, but with a high sensitivity to chemotherapy

and with lasting remissions. In diagnosed patients with stages I and II there are prospects to recover by applying current therapeutic methods (*table 2*).

Table 2

Indolent and aggressive NHL comparative data

Criterion	Indolent NHL	Aggresive NHL
General information	It practically does not develop in children up to the age of 12-14 years. Morbidity increases with age, reaching its maximum at the age of over 60.	In children, only the aggressive types develop
Tumor development and growth	The growth of the tumor is slow but with the major tendency of generalization.	Local rapid growth.
Evolution	They are frequently diagnosed in generalized stages. Most often, bone marrow interest occurs (60-65%).	Patients are more often diagnosed at local stages. Bone marrow is rarely affected (20-25%). In contrast to indolent NHL, more frequent CNS features occur.
Treatment	In some cases there is the „watch-and-wait" awaiting strategy applied.	It starts with making a diagnosis
Treatment response	Moderate response to treatment, more often only partial remission being obtained. Healing rarely occurs.	High reaction to current therapy. In stages I-II up to 85-90% with healing possibility.

In 52-70% of cases the NHL onset takes place in the lymph nodes, that is why the clinical signs is lymphadenopathy [20, 21]. Frequently the primary tumor outbreak of NHL occurs extranodally-30-45%. NHL from the extranodal locations more often develops in the pharyngeal lymphatic ring (19-21%), gastrointestinal tract (17-19%), spleen (4-6%). NHL can develop primarily in any organ or tissue where lymphoid tissue is present. The frequency of other locations is from 1% to 2%.

Bone marrow is frequently affected. More often the bone marrow is affected in indolent NHLs (60-65%). Less frequently (20-25%) – in aggressive NHL. In the NHL with the onset in the Waldeyer lymphatic

ring, the palatal tonsils are affected more often in adults, while in children – the nasopharyngeal tonsil. In NHL with primary gastrointestinal tract involvement the stomach is most commonly affected in adults, while in children – the iliocecal region of the intestine.

In indolent NHL with the onset in the peripheral lymph nodes there is a succession in the spread of the tumor process in the neighboring lymph nodes. In the NHL with extranodal localization in both the indolent and aggressive variants, metastasis in the regional lymph nodes occurs at the initial stages, depending on the location of the primary outbreak. For example, in the case of primary involvement of the nasopharyngeal tonsil, metastases may initially be detected in the cervical lymph nodes, subsequently – in the bone marrow or in NHL with mediastinal onset, metastases may occur in the bone marrow or the CNS without affecting other groups of lymph nodes. In primitive splenic NHL, indolent variants predominate and the bone marrow is frequently affected afterwards or it can occur without affecting the regional lymph nodes.

Non-Hodgkin's lymphomas clinical picture

There are no specific NHL clinical signs. The NHL clinical picture depends on:

- localization of the primary outbreak,
- the degree of spread of the tumor process,
- morphological type.

In NHL with primary lymph node involvement the first sign is lymphadenopathy. The peripheral lymph nodes predominate, followed by the abdominal. The NHL onset occur rarely in the mediastinum. Initially a lymph node enlarges and then other lymph nodes appear sequentially in the same region and form the primary area (*Fig. 5*).

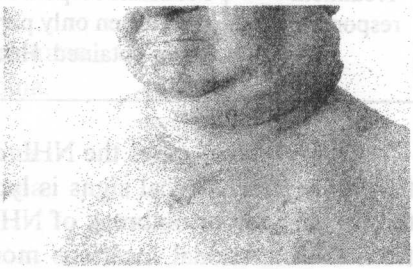


Fig. 5. Involvement of the left cervical, supraclavicular lymph nodes.

The clinical picture of NHL with primary mediastinal lymph node involvement depends on a tumor size. In the case of small dimensions, the patient is asymptomatic and can be identified occasionally

during prophylactic imaging research of the chest (*Fig. 6*). As the tumor process progresses, the clinical signs may appear, conditioned by the compression of the mediastinal organs: the airways, esophagus, large vessels. The patient complains of dry cough, dyspnea, dysphagia and facial edema, that is a sign of compression of the superior vena cava.

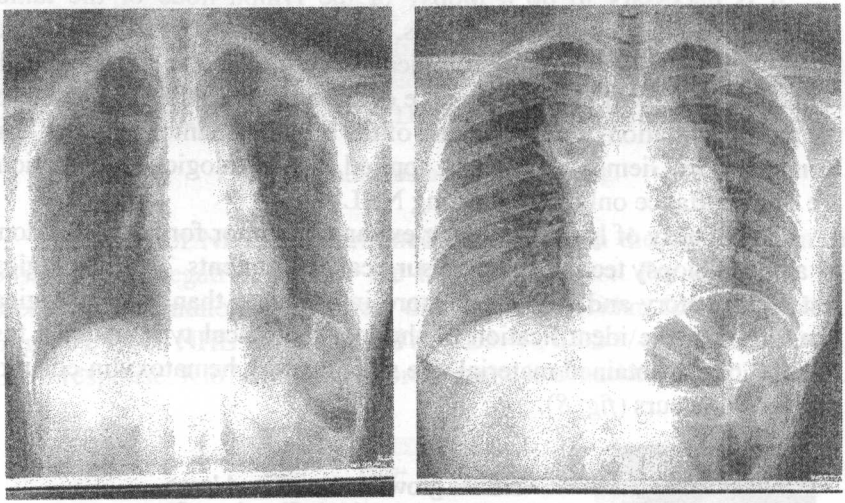


Fig. 6. Enlarged shadow of the mediastinum on a mediastinum tomography and chest X-ray.

NHL with the onset in the abdominal lymph nodes is asymptomatic as long as the lymph nodes are small and they can be detected only on USG and CT of the abdominal organs. Affected lymph nodes of large size can cause pain and signs of compression of the urinary tract, peripheral nerveswith dysfunctions of the organs of the abdominal cavity and small pelvis.

The clinical picture of the NHL with extranodal development is analogous to the clinical manifestations of a tumor of the respective organ – the Waldeyer lymphatic ring, gastrointestinal tract, spleen, bone, soft tissue, CNS, skin and so on (*Fig. 7*).

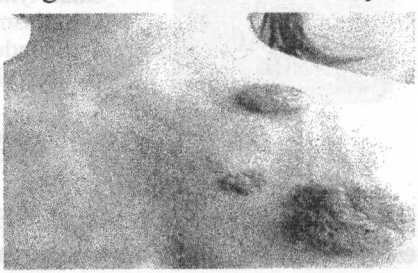


Fig. 7. Skin involvement in NHL.

Non-Hodgkin's lymphomas diagnosis

The diagnosis of NHL is complex and it is made based on a number of tests. The follouing methods are used in making the diagnosis of NHL:

Morphology: cytology and histology

It is necessary to do a biopsy of the lymph node or the tumor formation for the morphological tests. It is important to remove the larger lymph nodes with the morphological structure of the NHL already formed. Cytological preparations are obtained as a result of puncture of the tumor formation or one puncture of the biopathic tumor imprints. The Romanovschi-Giemsa staining is applied, but cytological preparations are of importance only in suspecting NHL.

The byopsy of lymph nodes or extranodal tumor formations is done by an open biopsy technique in the surgical departments. The histological test is obligatory and it is much more informative than the cytological one allowing the identification of the morphological type. After a fast fixation of the obtained material, the staining with hematoxylin-eosin or azur-eosin occurs (*fig. 8*).

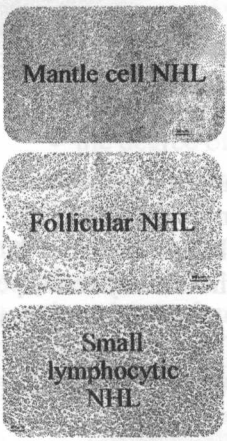


Fig. 8. Histological testing of various types of NHL.

Immunohistochemistry

Determining the types of NHL based on morphological study is extremely difficult. Immunohistochemical investigations in the diagnosis of NHL predict the use of the antibody panel according to the supposed diagnosis, as a result of the histological examination performed initially.

Anti-CD19, CD20 monoclonal antibodies are used to confirm the B-cell line of lymphoid cells and the CD5, CD10, CD3, CD23, CD25, CD22 required for the differential diagnosis of the NHL subtypes (*Fig. 9*).

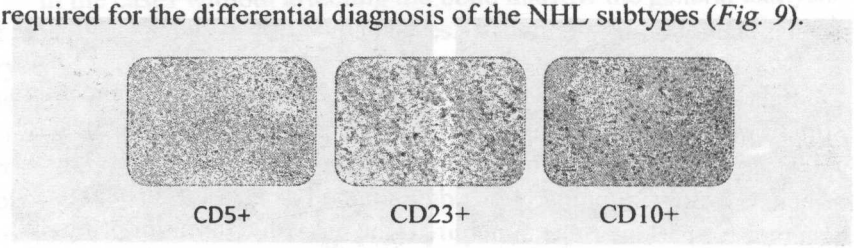


Fig. 9. Immunohistochemical testing.

The type of NHL is determined depending on the combination of positive and negative data of the histologycal test. For example, we present the immunohistochemical diagnostic algorithm for B-cell NHL (*Fig. 10*). T-cell NHL is caracterized by CD3 +/-, CD2 +/-, CD5 +/-, CD4 +, CD8- response. Ki67 is a nuclear protein and is a marker of proliferation.

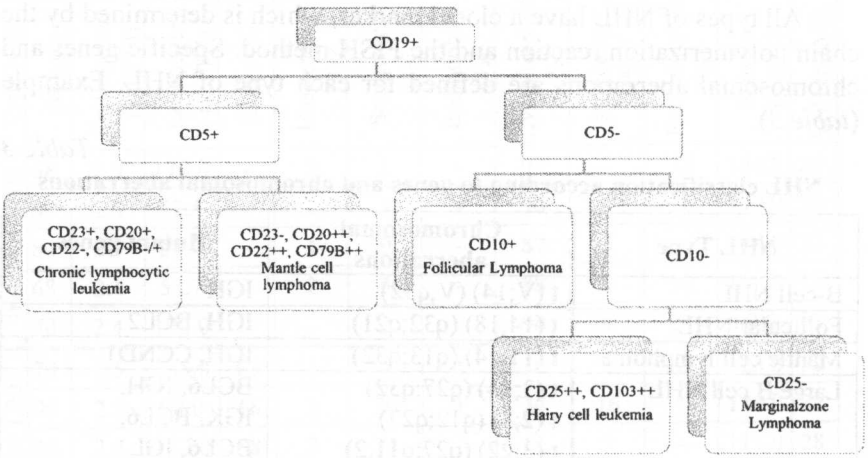


Fig. 10. Immunohistochemical diagnosis of B-cell NHL.

Flow cytometry

It allows the rapid simultaneous evaluation of the molecular parameters in heterogeneous cellular suspensions. It is a rapid measurement of cells in suspension that pass, one by one through the detection system.

This testing method allows the detection of the cellular and molecular phenotypic profiles associated with different pathologies (*fig. 11*).

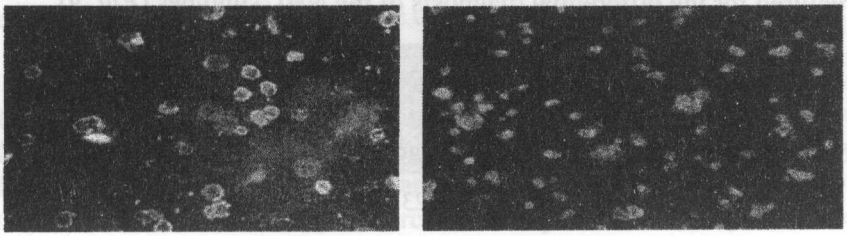


Fig. 11. Lymphocytes marked with monoclonal antibodies in the dark field target 40x / 0.65 plane.

Molecular biology

The molecular genetic test of NHL contributes to:

a) making the diagnosis,

b) estimation of the prognosis,

c) evidence of lymphoma evolution.

All types of NHL have a clonal marker, which is determined by the chain polymerization reaction and the FISH method. Specific genes and chromosomal aberrations are defined for each type of NHL. Example (*table 3*).

Table 3

NHL classification according to genes and chromosomal aberrations

NHL Type	Chromosomal aberrations	Mutant genes
B-cell NHL	t (V;14) (V;q32)	IGH
Follicular NHL	t (14;18) (q32;q21)	IGH, BCL2
Mantle cell lymphoma	t (11;14) (q13;q32)	IGH, CCND1
Large B cell NHL	t (3;14) (q27;q32) t (2;3) (q12;q27) t (3;22) (q27;q11,2)	BCL6, IGH, IGK, BCL6, BCL6, IGL
MALT Lymphoma	t (11;18) (q21;q21) t (14;18) (q32;q21)	AP12, MALT IGH, MALT

Hematological changes in non-Hodgkin's lymphomas

In the cases without affecting the bone marrow the general analysis of the blood is without specific changes. There may also be an increased erythrocyte sedimentation rate (ESH), which characterizes the activity of the tumor process. The complication of NHL with secondary auto-immune hemolytic anemia results in decreased hemoglobin content and red blood cell count, the occurrence of reticulocytosis. In the cases of complication with autoimmune thrombocytopenia in the general blood analysis there is and / or thrombocytopenia. Specific changes in the general blood analysis occur in patients with affected bone marrow and leukemization. In the cases of indolent NHL, prolymphocytes appear in the complete blood count, the percentage of lymphocytes increases, and in aggressive NHL – the percentage of blast cells. Metaplastic anemia and thrombocytopenia develop (*table 4*).

Table 4

Complete blood counte in NHL with bone marrow involvement and leukemization

Type NHL	Hb (g/l)	Erythrocytes (x 10^{12}/l)	Leukocytes (x 10^{9}/l)	Blasts (%)	Unsegment. (%)	Segmented (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Reticulocytes (%)	Platelets (x 10^{9}/l)	VSH (mm/h)
Indolent LNH	68	2.4	170.0	-	2	1	-	**97**	-	35	144.0	20
	80	2.9	52.5	-	1	3	-	**96**	-	20	197.0	30
	84	2.9	27.0	-	1	9	-	**87**	3	-	174.0	32
	68	2.4	53.7	-	2	5	-	**88**	5	10	160.0	14
	70	2.4	170.0	-	-	2	-	**94**	4	24	60.0	73
Agressive LNH	70	2.5	135.0	**63**	1	4	1	26	3	2	123.0	52
	90	2.9	90.0	**16**	3	30	1	34	16	-	180.0	32
	84	2.4	142.0	**58**	2	24	-	11	5	-	111.0	28
	59	2.0	169.0	**71**	-	5	-	10	14	-	85.0	74
	91	3.0	53.0	**18**	4	27	2	38	11	2	156.0	34

The number of leukocytes in both indolent and aggressive NHL does not correlate with the size of the tumor component, the latter being larger.

The importance of trepanobiopsy in non-Hodgkin's lymphomas

A bone marrow lesion is confirmed by medullary puncture, which reveals the presence of cells characteristic of the morphological type found in the patient. Trepanobiopsy detects foci of bone marrow lesion. Trepanobiopsy of the iliac bone is the histological investigation of the bone marrow.

This procedure consists in removing a bone portion that contains bone marrow. Bone marrow samples are usually taken at the level of the superior posterior or anterior superior iliac crest.

In NHL the biopsy of the iliac bone is indicated for:

1. Determining the degree of spread of the tumor process
2. Assessment of spinal cord lesion stage

Trepanobiopsy also is of a diagnostic significance when tumor formations are not accessible for biopsy (involvement of the abdominal lymph nodes, spleen) and the bone marrow is affected.

The morphological picture of the bone marrow in case of NHL lesion corresponds to the NHL type.

In small lymphocytic NHL with the invasion into bone marrow, histological samples prepared from the bone marrow are characterized by small lymphoid cells with narrow cytoplasm, the nucleus with condensed chromatin, which produces follicular foci of different sizes, located in the medullary cavities. The histological picture formed by the lymphoid cells is homogeneous with well-defined foci. The tissue around them consists of myeloid elements at different stages of differentiation.

In marginal zone NHL with bone marrow lesion, there are foci of infiltration of bone marrow with lymphoid cells which in biopsy have the character of mature cells with compact nucleus chromatin, without nucleoli, with narrow cytoplasm.

In follicular NHL with bone marrow involvement on regular cellularity background, there is evidence of dissemination of small and medium size lymphoid cells, sometimes groups of lymphoid cells without the formation of certain structures occur. In some cases, a group of lymphoid cells resembles the structure of a follicle (*fig. 12*).

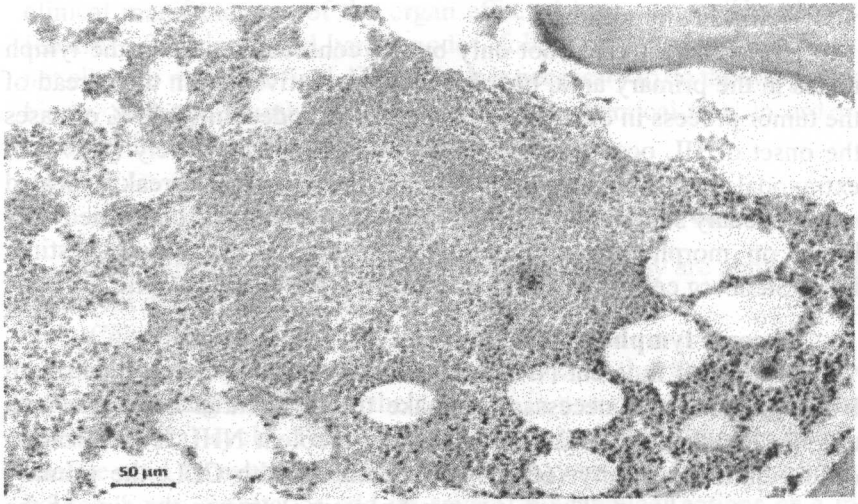


Fig. 12. Bone marrow metastasis of follicular NHL. Formation of pseudofollicles. Hematoxylin and eosin staining, X 70.

In mantle cell NHL with the involvement of the bone marrow, there are fields of lymphoid cells larger than the diffused small lymphocytes. Lymphoblastic NHL with bone marrow involvement is characterized by infiltration with lymphoblasts, that do not differ.

Differential diagnosis of non-Hodgkin's lymphomas

The differential diagnosis of NHL is necessary to be performed with:

- Reactive hyperplasia of the lymph nodes
- Hodgkin's lymphoma (HL)
- Chronic lymphocytic leukemia
- Cancer metastases in the lymph nodes

Reactive hyperplasia of the lymph nodes

Reactive hyperplasia of the lymph nodes is the most common form of benign lymphadenopathy. Reactive hyperplasia has a regional lymph node response in the case of a focus of infection. In contrast to NHL, in this case there is a lack of consecutive lymph nodes: they grow concomitantly in one area or in more anatomical areas, they are the same size. The main impact area is absent. In dynamics, the dimensions of the enlarged lymph nodes decrease.

Hodgkin's lymphoma

HL is characterized not only by the consecutiveness in the lymph nodes in the primary area, but also the consecutiveness in the spread of the tumor process in other areas of the lymph nodes. In 98-99% of cases the onset of HL occurs in the lymph nodes and very rarely (1-2%) in extranodal sites, in contrast to NHL where the primary outbreak is located in extranodaly site in 30-45%. The final diagnosis can be confirmed only based on morphological, immunohistochemical, cytogenetic testing. Reed-Stenberg cells with CD15 and CD30 positive are specific for HL.

Chronic lymphocytic leukemia

In cases of indolent NHL with the bone marrow involvement with leukemization, it is necessary to make the differential diagnosis with chronic lymphocytic leukemia (CLL). In indolent NHL leukemization occurs quite frequently (60-65%). In patients with CLL, the primary tumor area is absent. There is a synchronicity between the size of the lymph nodes and the number of leukocytes, but in indolent NHL with leukemization the synchronicity lacks. The correlation between the number of leukocytes and the size of the tumor formations that are larger than the number of leukocytes. In CLL the percentage of lymphocytes in the hemogram corresponds to that of the bone marrow. The lymphocytes are small with the condensed nucleus chromatin, narrow cytoplasm. They are shadows of semi-destroyed lymphocytes called nuclear or Gumpreht shadows.

Peripheral blood lymphocytosis corresponds to bone marrow lymphocytes. In patients with indolent NHL with leukemization according to the morphological structure, the lymphocytes correspond more to the prolymphocytes and their percentage in the peripheral blood differs from that of the bone marrow. In the differential diagnosis, immunohistochemical, cytogenetic and molecular biology tests are of particular importance. Positive CD5 and CD23 are characteristic of CLL. Cytogenetics determines the deletion of the long band 11q-, 13q-, 16q-.

Cancer metastases in the lymph nodes

Metastasis is the dissemination of cancer cells from the primary tumor focus and the formation of new colonies of distant tumor cells in the invaded tissues. In this case the lymph node involvement is secondary. Cancer metastases in the lymph nodes are usually associated with

clinical manifestations of the organ affected by a tumor. The physical features of the increased lymph nodes following cancer metastases do not allow to make the final diagnosis. It is necessary to do the lymph node biopsy with the morphological, immunohistochemical tests in order to confirm the cancer metastases in the lymph nodes.

Principles of non-Hodgkin's lymphomas treatment

Chemotherapy, immunotherapy and radiotherapy are applied in the treatment of NHL .

Chemotherapy

Chemotherapy is used to destroy tumor cells that develop and grow rapidly, slowing or stopping their growth in one or more stages of their developmental cycle. The cytostatic effect is due to the disruption of nucleic acid biosynthesis (DNA and RNA) and proteins by antimetabolites. Some cytostatics add up several biochemical actions or a mechanism of action at the molecular level. As some drugs are more effective than taken together, more often the treatment consists of administering several chemopreparations. This method is called polychemotherapy or combination chemotherapy. Polychemotherapy destroys more malignant cells than each of them taken separately, so it has synergistic effect, also called additive. The toxic effects of chemotherapy has an impact on all cells with high replication speed, such as bone marrow, mucosal cells, germ cells and so on.

Immunotherapy

The term immunotherapy is used for anti-tumor therapy that uses the immune system to recognize and destroy malignant cells. Immunotherapy is the use of monoclonal antibodies that recognize and then bind to antigens that are overexpressed on the cell surface. The action mechanisms of monoclonal antibodies are:

- Attachment of ligands or receptors, thus disrupting the essential processes of tumor cells
- Transporting radioisotopes or toxins to the target cells (conjugated monoclonal antibodies)

Radiotherapy

The principle of action of radiotherapy is the irradiation with gamma or X-ray of small regions with low doses to reduce the adverse effects and to protect the healthy tissues, but without reducing the therapeutic

effectiveness. Malignant lymphomas are considered radiosensitive tumors.

Hematopoietic stem cell transplantation

Hematopoietic stem cell (HSC) transplantation is applied to restore hematopoiesis after myelosuppressive treatment, especially chemotherapeutic one. Two kinds of transplantation should be differentiated:

1. autotransplantation.
2. allotransplantation.

The treatment of NHL is individualized and is according to the morphological type, the location of the primary tumor focus, clinical stage, as well as depending on the prognostic factors. Therapy management can range from a simple dynamic clinico-hematological monitoring to aggressive treatment with polychemotherapy, radiotherapy, including hematopoietic stem cell transplantation .

The International Prognostic Index (IPI) [22, 23, 24, 25] is characteristic of all types of NHL except follicular NHL, for which the Follicular Lymphoma International Prognostic Index (FLIPI) is determined [25, 26, 27, 28, 29].

The unfavorable prognostic factors that serve as the basis for the IPI creation are:

- age > 60 years,
- generalized stages (III-IV) according to the Ann Arbor Clinical Classification,
- the presence of more extranodal foci (than one outbreak),
- the general condition of the patient according to the levels proposed by the ECOG (levels 2-4) [30, 31],
- increased the LDH level.

Each factor is a point. According to the score, the patients are included in one of the 4 risk groups:

low risk – the absence or presence of only one unfavorable factor (0-1 points),

intermediate risk – low, the presence of 2 factors (2 points),

intermediate risk – high, the presence of 3 factors (3 points),

high risk – the presence of 4 and more factors (4-5 points).

The FLIPI includes:

- the age over 60,
- clinical stages III-IV according to the Ann Arbor Clinical Classification,

- hemoglobin content below 120 g / l,
- the number of affected lymph nodes greater than 4,
- increased LDH level.

According to the number of adverse signs, three prognostic groups are formed:

- **low risk** (0-1 signs of poor prognosis),
- **intermediate risk** (2 signs),
- **high risk** (3 and more unfavorable signs).

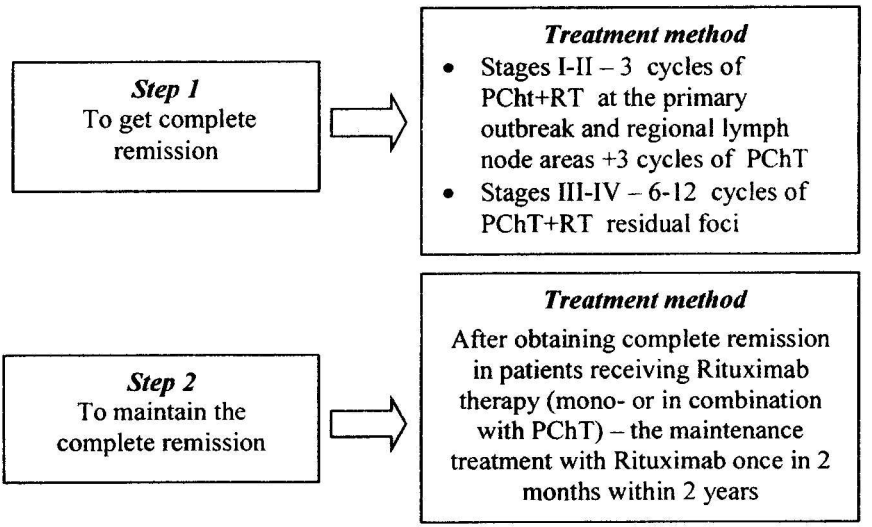
Table 5

ECOG Performance status

Status	Definition
0	Normal activity
1	The presence of symptoms, but the patient is monitored on an outpatient basis
2	< 50% of time is spent in bed
3	More than 50% of time is spent in bed
4	100% bed dependent patients

Explanatory note – ECOG (the Eastern Cooperative Oncology Group).

Non-Hodgkin's Lymphoma Treatment Algorithm



Treatment algorithm of indolent non-Hodgkin's lymphomas

In stages I and II, a combined treatment is administered, which includes 3 cycles of PChT + RT on the foci + 3 cycles of PChT. PChT schemes used in indolent NHLs at local stages are:

- R-COP,
- R-CVLP,
- R-LVPP,
- R-CHOP.

The survival of over 5 years as a result of this treatment constitutes 63-82% of cases. Sometimes when there are contraindications for PChT, only MChT can be administered. MChT with Chlorambucil, Cyclophosphamide or Vincristine are used in generalized stages III and IV in cases of indolent clinical evolution in persons over 65 and those with concomitant pathologies that represent contraindications for PChT. In cases when there are no contraindications for PChT, 6-8-12 cycles are applied according to the following schemes:

- R-CVP,
- R-COP,
- R-CHOP,
- R-CVLP,
- R-LVPP.

Radiation therapy (RT) can also be administered. In stage III – in all groups of lymph nodes, in stage IV – in residual foci.

In the treatment of indolent NHL, Fludarabine – MChT or in combination with other preparations can be used: FC, R-FC, R-FND, R-FCM. The treatment with monoclonal antibodies (anti CD20-Rituximab) as monotherapy is also used in indolent NHL.

Treatment algorithm in aggressive non-Hodgkin's lymphomas

In stages **I** and **II**, a combined treatment is administered which includes 3 cycles of PChT + RT on the foci + 3 cycles of PChT. The PChT scheme used in aggressive NHLs at local stages is:

- R-CHOP
- R-CAP

In generalized stages **III** and **IV**, 6-8-12 cycles of PChT R-CHOP are applied. RT is applied to lymph node groups that do not regress in the PChT background.

In cases of primary involvement of the mediastinal lymph nodes, in patients up to 50 years of age, the prophylaxis of neuroleukemia is also

performed with intrathecal administration of methotrexate 12.5 mg/m^2, cytarabine 30 mg/m^2, dexamethasone 4 mg. In case of bone marrow involvement, the treatment is performed according to the principles of treatment of acute leukemias.

In primary resistant and early relapse cases, intensive PChT schemes followed by hemopoietic stem cell autotransplantation are indicated:

- R-CHOEP
- R-BCHOP
- R-BCHOEP
- R-DHAP

Evolution and prognosis

- The evolution of NHL is severe leading to the dissemination of the malignant process in the lymph nodes, in vital organelles with the development of polyorganic insufficiency and lethal end.
- Indolent NHLs although with relatively rapid generalization have a longer evolution and survival.
- Aggressive NHLs have a severe prognosis, depending on the degree of spread. In patients with local stages (I and II) long-term complete remissions can be achieved, and in the generalized stages (III and IV) the application of modern treatments has increased the percentage of complete remissions with prolonged survival.
- The association of autoimmune complications, predominantly autoimmune hemolytic anemia and infectious complications is another factor aggravating the prognosis and quality of life.
- Bone marrow and CNS involvement are severe prognostic factors.

Clinical case

Patient A., 45 years old, was hospitalized complaining of general asthenia, feeling of weight in the left hypochondrium. He has been considered to be ill for the last 6 months, when the so-called complaints appeared and gradually intensified.

Objective examination: the general state of average severity. Pale pink skin. Peripheral edema is absent. The peripheral lymph nodes are not palpable. On lung percussion – pulmonary sound, auscultation – vesicular murmur. Rhythmic heart sounds, sound heart beat with heart rate-

80 / minute, AP-120 / 60 mmHg. The abdomen is soft, painless on touch. The liver is not palpable. The spleen exceeds the costal rim by 5 cm, and is of hard consistency.

Complete Blood Count

Hematological parameters	Indices	Unit of measurement	Norm
Leukocyte number	5.1	mii/μL	4-10
Red blood cell number	3.6	mil/μL	3.8-5.1
Hemoglobin (Hb)	12	g/dL	120-155
Reticulocytes	1	‰	2-10
Number of platelets	410	mii/μL	150-450
Neutrophil	60	%	45-80
Lymphocyte	30	%	20-55
Monocyte	10	%	6-11
Eosinophil	2	%	0-5
Basophil	0	%	0-1
Erythrocyte sedimentation rate (ESR)	35	mm/h	5-15

Biochemical indices

Biochemical parameters	Indices	Unit of measurement	Norm
ALT(alanine aminotransferase)	35	U/l	8-40
AST(aspartate aminotransferase)	24	U/l	8-40
Total bilirubin	16	μmoli/l	2-17
Direct bilirubin	5	μmoli/l	0-5
Indirect bilirubin	11	μmoli/l	2-12
Urea	5,3	μmol/l	4.4-8.8
Creatinine	61	μmol/l	53-106
LDH	245	U/l	45-90

USG of the abdominal cavity

Liver RL (right lobe) – 115 mm, LL (left lobe) – 70 mm, the portal vein – 9 mm. The contour is regular, the parenchyma is homogeneous, average echogenicity. The gallbladder is of regular form, normal size with multiple gallstones. The pancreas is 30x15x28 mm, regular contour, homogeneous parenchyma, average echogenicity. The spleen is 240x135 mm, non-homogeneous, on the median part of the spleen, more on the lower pole there is a non-homogeneous tumor formation, round

with a diameter of 7.0 cm. The lienal vein-5.8mm. Conclusion. Splenomegaly. Spleen mass. Chronic cholelythiasis.

Make a preliminary diagnosis.

1. Indicate the tests necessary to confirm the final diagnosis
2. Determine the treatment strategy.

Control tests

S In which of the following types of non-Hodgkin's lymphomas does the secondary involvement of the central nervous system predominate:

A. Small lymphocytic Lymphoma
B. Lymphoplasmacytic Lymphoma
C. Follicular Lymphoma
D. Marginal zone Lymphoma
E. Lymphoblastic Lymphoma

S The complex investigation of a patient with non-Hodgkin's lymphoma revealed: the enlargement of the cervical lymph nodes on both sides, in the left axillary zone, mediastinum, with signs of general intoxication. Choose the clinical stage:

A. I A
B. II A
C. II B
D. III A
E. III B

S The important criterion for suspecting non-Hodgkin's lymphoma is:

A. Weight loss
B. Fever
C. Consecutive appearance of lymph nodes
D. Anemic syndrome
E. Hemorrhagic syndrome

S Most commonly non-Hodgkin's primary lymphomas affect:

A. Lymph nodes
B. The spleen
C. The gastrointestinal tract
D. The pharyngeal lymphatic ring
E. Lung tissue

S In non-Hodgkin's lymphomas the following primary lymph node injury predominates:

A. Cervical
B. Axillary
C. Inguinal
D. Mediastinal
E. Retroperitoneal

S Choose the type of non-Hodgkin's lymphoma characterized by the most common bone marrow involvement with leukemization:

A. Lymphoblastic Lymphoma
B. Immunoblastic Lymphoma
C. Small lymphocytic Lymphoma
D. Lymphoplasmacytic Lymphoma
E. Follicular Lymphoma

S The clinical manifestation of non-Hodgkin's Lymphoma is:

A. Anemic syndrome
B. Hemorrhagic syndrome
C. Number of leukocytes
D. Morphological type, localization of the primary tumor focus and clinical stage
E. None of those listed above

S In generalized stages (III-IV) of aggressive non-Hodgkin's lymphomas, the optimal treatment method is:

A. Surgical treatment
B. Monochemotherapy
C. Polychemotherapy
D. Radiotherapy
E. Surgical treatment and radiotherapy

S In the local (I-II) stages of non-Hodgkin's lymphomas, the optimal treatment method is:

A. Monochemotherapy
B. Radiotherapy after the radical program
C. Surgical treatment

D. Polychemotherapy
E. Combined treatment (3 courses of polychemotherapy + radiotherapy on tumor focus and regional lymph nodes + 3 courses of polychemotherapy)

S The final diagnosis of non-Hodgkin's lymphoma is determined by:
A. Hemolithogram investigation
B. Histological and immunohistochemical examinations of tumor mass
C. Computed tomography
D. Radiological examination
E. Ultrasound examination

S Choose an important criterion of non-Hodgkin's lymphoma:
A. Concomitant enlargement of all groups of peripheral lymph nodes
B. The presence of hemorrhagic syndrome
C. The presence of anemic syndrome
D. Hypertrophy of the lymph nodes
E. Consecutive appearance of lymph nodes

S In cases of non-Hodgkin's lymphoma leukemization, the lymphoblastic blood picture may be:
A. Within the norm
B. Similar to acute leukemia
C. Similar to chronic lymphocytic leukemia
D. Similar to chronic granulocytic leukemia
E. Similar to chronic monocytic leukemia

S Choose the specific change in the clinical picture of non-Hodgkin's lymphoma with primary involvement of the palatal tonsils:
A. Pain in the throat
B. The difficulty of the swallowing act
C. The sense of a foreign body in the throat
D. Enlargement of the palatal tonsils
E. None of the listed above

S The cervical lymph node enlargement on the left and retroperitoneal sides was found as a result of a complex examination of a patient with non-Hodgkin's lymphoma. Define the clinical stage:

A. II A
B. II B
C. III A
D. III B
E. IV A

S Choose the change in the general blood test in non-Hodgkin's lymphomas without affecting the bone marrow:

A. Blastosis
B. Leukopenia
C. Hyperthrombocytosis
D. Lymphocytosis
E. None of the above

S The diagnosis of non-Hodgkin's lymphoma can be made only after:

A. General blood analysis
B. Radiological examination
C. Morphological and immunohistochemical testing of the removed tumor mass
D. Ultrasound examination
E. Computed tomography

S. In the case of cervical lymphadenopathy with suspected non-Hodgkin's lymphoma, the most important test is:

A. The ENT exam
B. Examination of the dentist
C. Chest X-ray
D. Lymph node biopsy
E. Ultrasound examination

S Clinical manifestations of non-Hodgkin's lymphoma depend on:

A. Changes in the complete blood count
B. Location of specific disease foci and the disease stage
C. Changes in myelogram
D. Age
E. None of the above

S The final diagnosis of non-Hodgkin's lymphoma with the primary focus in the mediastinum is made based on:

A. Radiological examination
B. Computed tomography
C. Complete blood count
D. Thoracotomy with morphological test of the mediastinal tumor formation
E. Sternal puncture

S The final diagnosis of non-Hodgkin's lymphoma is made on:

A. Complete blood count
B. Histological test of the removed tumor mass
C. Sternal puncture
D. Radiological examination
E. Ultrasound examination

C The presence of symptoms of general intoxication (B) in non-Hodgkin's lymphoma implies:

A. Poor prognosis
B. More aggressive evolution of the disease
C. Favorable prognosis
D. Favorable disease progression
E. High treatment efficacy

C The morphological types with a low degree of malignancy of non Hodgkins' lymphomas are:

A. Microlymphoblastic
B. Macrolymphoblastic
C. Prolymphocytic
D. Lymphoplasmacytic
E. Immunoblastic

C The following statements about non-Hodgkin's lymphomas are true:

A. The primary focus of the tumor may develop in any organ, composed of lymphatic tissue
B. The primary focus frequently develops in lung tissue
C. It never affects the bone marrow

D. Morbidity increases with age
E. The primary focus develops rarely in the gastrointestinal tract

C The following statements about for indolent non-Hodgkin's lymphomas are true:

A. Aggressive evolution
B. Bone marrow is frequently affected
C. The central nervous system is affected quite frequently
D. The primary focus develops commonly in the spleen
E. Extranodal locations occur very rarely

C The diagnosis of NHL with isolated mediastinal lymph node involvement is confirmed by:

A. Radiological examination
B. Mediastinoscopy with biopsy
C. Ultrasound examination
D. Exploratory thoracotomy with biopsy
E. Computed tomography

C The morphological variants of non-Hodgkin's lymphoma with high degree of malignancy are:

A. Lymphoblastic
B. Prolymphocytic
C. Lymphocytic
D. Immunoblastic
E. Lymphoplasmocytic

C Which of the following factors is indicative of an unfavorable evolution of non-Hodgkin's lymphoma:

A. Prolymphocytic variant
B. Leukemization of non-Hogkin's lymphoma with blast cells
C. Generalized stages
D. Local stages
E. Primary local stomach involvement

C The most common primary extranodal locations of non-Hodgkin's lymphoma are:

A. Lung tissue
B. Gastrointestinal tract

C. Central nervous system
D. Bones
E. Pharyngeal lymphatic ring

C Which of the following statements about non-Hodgkin's lymphomas is true:

A. The choice of the polychemotherapy scheme is according to the morphological type
B. The choice of the polychemotherapy scheme does not depend on the morphological type
C. The bone marrow involvement occurs more frequently than in Hodgkin's disease
D. The extranodal onset occurs in exceptional cases
E. The evolution of non-Hodgkin's lymphomas is more aggressive than that of Hodgkin's disease

C The factors that determine the treatment tactics in non-Hodgkin's lymphoma are:

A. The morphological type
B. The stage of the disease
C. Alkaline phosphatase activity
D. Sex
E. Localization of the primary tumor outbreak

C Non-Hodgkin's lymphoblastic lymphoma with leukemization is characterized by:

A. The general blood analysis count within the norm
B. Blastosis in the peripheral blood
C. Depression of normal hematopoiesis
D. Blastosis in the medullary puncture
E. The spinal cord puncture within the norm

Bibliography

1. **Campo E., Swerdlov S., Harris. et all.** The 2008 WHO Classification of lymphoid neoplasms and beynd: evolung concept and practical applications. Blood. 2011; 117: 5019-5032.
2. **Buruiană S.** Aspecte clinice, hematologice și imunohistochimice ale limfoamelor non-Hodgkin foliculare: studiu prospectiv, descriptiv. Moldovan Journal of Health Sciences. Revista de Științe ale Sănătății din Moldova. 2016, nr. 10(4), p.53-60.
3. **Galafteon O., Cândea M., Demian M. ș.a.** Îndrumător pentru stagii clinice de Medicina Internă-Hematologie. 2017, p. 56-59.
4. **Corcimaru I.** Hematologie clinică. 2007, p. 252-279.
5. **Buruiană S.** Aspectele clinice, hematologice și imunohistochimice ale limfoamelor non-Hodgkin limfocitare din limfocite mici. Simpozionul „Vigilența oncologică în activitatea medicală; depistarea precoce și tratamentul tumorilor", dedicate aniversării – 40 de ani de activitate a Catedrei de oncologie, hematologie și radioterapie a IP USMF „Nicolae Testemițanu". INFO-MED. 2016, nr.2(28), p. 52-58.
6. **Немцова М., Майорова М.** Использование достижений современных геномных технологий при лимфомах. Клиническая онкогематология. 2016; 9 (3) : 265-270.
7. **Intlekofer A., Younes A.** Precision therapy for lymphoma – current state and future directions. Nat. Rev. Clin. Oncol. 2014; 11(10): 585-596.
8. Non-Hodgkin's Lymphoma in Children Detailed Guide. htpp://www.cancer.org/docroot/CRI/content/CRI_2_4_7xCRC_Non Hodgkins_Lymphoma_in_Children_PDF.asp.
9. **Robu M.** Limfoamele nehodgkiniene. Chișinău, 2003, 55.
10. **Chiu B.C.H., Hon N.** Epidemiology and etiology of non-Hodgkin lymphoma. Non-Hodgkin Lymphoma-Springer Cham, 2015, 1-25.
11. **Поддубная И.В.** Неходжкинские лимфомы. Клиническая онкогематология. Москва, «Медицина», 2011, с. 336-375.
12. **Луговская С. А., Почтарь М. Е., Тупицин Н. Н.** Иммунофенотипирование в диагностике гемобластозов. Москва. 2005; 166 стр.
13. **Джалилов А. Ф.** Неходжкенские лимфомы: основы классификации и иммуноцитохимической диагностики. Онкология. 2013; 15 (4) : 264-272.

14. **Galafteon O., Cândea M., Demian M. ş.a.** Curs de Medicina Internă. Bolile Hematologice. 2014, p. 112-124.
15. **Marquardt N., Beziat V., Nystrom S.** Cutting Edge: Identification and Characterization of Human Intrathepatic CD $^{49+}$ NK Cells. The Journal of Immunology. 2015; 194 (6): 2467-2471.
16. **Swerdlov S.** et all. The 2016 Revision of the WHO Classification of lymphoid neoplasms. BLOOD. 2016; 127(20): 2375-2390.
17. **Miron L.** Limfoamele maligne Non-Hodgkiniene. Suport de curs. Facultatea de Medicină. Oncologie. UMF. IAŞI. 2014; 46-88.
18. **Rhone-Alpes.** Lymphomes non hodgkiniens. Etude qualitative exploratoire molphy. Modes de vie, hemopathies lymphoides, hygiene. 2014. Avril; 17-20.
19. **Buruiană S.** Actualităţi în studierea limfoamelor non-Hodgkin indolente. Anale ştiinţifice ale USMF „N. Testemiţanu". 2013; Ediţia XIV (3). Probleme actuale în medicina internă : 470-477.
20. **Mehrdad Payandeh, Masoud Sadegi, Ali Shahriari-Ahmadi et al.** The survival of Nodal non-Hodgkin's lymphoma patients in the West of Iran. American Journal of Cancer Prevention. 2015; 3(5): 103-105.
21. **Shankland R.R., James O.** Armitage, Barry W. Hancock. Non-Hodgkin lymphoma. The Lancet. 2012; 380: 9844: 848-857.
22. **Zhou Z., Sehn LH., Rademaker AW., et al.** An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B- cell lymphoma treted in the rituximab era. Blood. 2014; 123 (6) : 837-842.
23. **Lee Hong Ghi, Kim Sung-Yong, Kim Inho et al.** Prediction of survival by applying current prognostic models in diffuse large B- cell lymphoma treated with R- CHOP followed by autologous transplantation. Blood Res. 2015; 50 (3) : 160-166.
24. **Huang H.H., Xiao F., Chen F. et al.** Reassessment of the prognostic value of the International Prognostic Index and the International revised. Exp. Ther Med. 2012; 4 (3) : 475-480.
25. **Ndiaye Faton Samba Diago, Seynabou Fall, Atoumane Faye et al.** Prognostic factors of non-Hodgkins lymphoma: retrospective study in unit blood service of the internal medicine dantec in Dakar (Senegal). Open Journal of hematology. 2015; 6 :1-6.
26. **Maeng Chi Hoon, Ahn Sung Woo, Seong-Yoon Ryu, et al.** Treatment outcomes and clinical reverance of the Follicular Lymphoma. International Prognostic Index in Korean follicular lymphoma patients treated with chemotherapy. Korean J. Intern Med. 2016; 31 (3) : 560-569.

27. **Lopez-Guillermo Armando.** A novel clinicogenetic prognostic score for follicular lymphoma. The Lancet. 2015; 16 (9) : 1011-1012.
28. **Sehn Laurie H., Fenske Timothy S., Laport Ginna G.** Follicular Lymphoma: Prognostic Factors, Conventional Therapies, and Hematopoetic cell Transplantation. Biology of Blood and Marrow Transplantation. 2012; 18 (1) : 82-91.
29. **W. Hiddemann and B. D. Cheson.** How we manage follicular lymphoma. Leukemia. 2014; 28 : 1388-1395.
30. **Kelly Ciara M. and Shahrokni Armin.** Moving beyond Karnofsky and ECOG Performance Status Assessments with New Technologies. J. Oncol. 2016; 2016 : 61886543.
31. **West Howard (Jack), MD; Jin Jill O., MD.** Performance Status in Patients with cancer. JAMA Oncol. 2015; 1 (7) : 998.