MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

***NICOLAE TESTEMIŢANU* STATE UNIVERSITY OF MEDICINE AND PHARMACY**

Department of Internal Medicine Hematology discipline

Robu Maria, Golub Aliona, Tomacinschii Victor, Buruiana Sanda

HODGKIN`S LYMPHOMA

(Methodological recommendations for students)

CHIŞINĂU
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Autori:

Robu Maria, dr. șt.med., conf. universitar
Golub Aliona, doctorand
Tomacinschii Victor, asistent universitar
Buruiană Sanda dr. șt. med., conf. universitar

Rcenzenți: *Musteață Larisa, dr. șt. med., conf. universitar,*
Catedra de oncologie
Corobceanu Nadejda, dr. șt. med., conf. universitar,
Catedra de oncologie

Redactor: *Lidia Seghienco-Ciobanu*

DESCRIEREA CIP A CAMEREI NAŢIONALE A CĂRŢII

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CONTENTS

LIST OF ABBREVIATIONS

CD	– cluster of differentiation
GHSG	– German Hodgkin`s Lymphoma Study Group
EORTC	– European Organization for Cancer Research and Treatment
NCIC / ECOG	– National Cancer Institute of Canada and Eastern Cooperative Oncology Group
HL	– Hodgkin's lymphoma
WHO	– World Health Organization
IMSP	– Public Health Care Institution
HIV	– human immunodeficiency virus
HTLV	– human T-lymphotropic virus
HHV	– human herpes virus
ESR	– erythrocyte sedimentation rate
EBV	– Ebstein-Barr virus
HLA	– human leukocyte antigen
BCL	– intracellular protein factor
CT	– computed tomography
PET / CT	– positron emission tomography/ computed tomography
PChT	– polychemotherapy
RT	– radiotherapy
HSC	– hematopoietic stem cells
ASCT	– autologous stem cell transplantation
NLPHL	– nodular lymphocyte-predominant Hodgkin's lymphoma

Hodgkin's lymphoma

Definition. Hodgkin's lymphoma (HL) is a malignant tumor that develops in the lymph tissue. This disease was first described by the English physician Thomas Hodgkin in 1832 (18). In 1865, Samuel Wilks proposed the name of Hodgkin's disease (35). Subsequently, the term lymphogranulematosis proposed in 1898 by Karl Sternberg and L. Rosenfield in 1899 was used. In 1998, at the IV International Symposium on Lymphogranulematosis, it was decided to name this disease Hodgkin's Lymphoma, which is still used today. HL is one of the first tumors with a high recovery potential. Patients with HL diagnosed in local stages (I - II) recover in 85% - 90% of cases [5, 11, 13, 34].

Preface. The methodological recommendations include the basic topics necessary for students to be able to suspect and establish the diagnosis of Hodgkin's lymphoma with the development of treatment principles. The methodological recommendations represent an accessible presentation of the subject of HL necessary for students to acquire knowledge about this disease. The major objective is to provide support to medical students. Notions and definitions will contribute to students` knowledge enrichment in the field and will be useful in knowledge assessment. Careful attention will be paid to the clinical activity of students at patient`s bedside, practical maneuvers, tests and situational problems on the given topic. To better acquire the material, the methodological recommendations have been completed with graphic presentations (tables, figures, diagrams), images, clinical cases, control tests.

The duration of the seminar is 5 hours.

Purpose of the seminar. To study epidemiology, etiology, pathogenesis, clinical manifestations, laboratory and instrumental methods of examination of patients for the diagnosis of HL, to determine the degree of spread of the malignant process and to acquire the principles of treatment.

Learning objectives

1. to obtain knowledge about the etiology, epidemiology and pathogenesis of HL; 2. to develop knowledge about the clinical, hematological, morphological and immunohistochemical issues of HL;

3. to acquire practical skills in establishing the diagnosis of HL;

4. to obtain knowledge about the differential diagnosis of HL;

5. to learn the general principles of treatment of patients with HL.

Setting of conducting seminars

1. *Nicolae Testemitanu* SUMPh, Hematology discipline

2. Hematology Units of the Hematology Department, PHCI Oncological Institute, Republic of Moldova

3. Hematological wards within the Diagnostic Consulting Center, PHCI Oncological Institute, Republic of Moldova

Teaching methods and materials

Teaching methods used. In order to effectively acquire knowledge and achieve objectives, the following didactic methods and procedures are used:

– material presentation, description, explanation, demonstration

– conversation, group discussion, problematization

– synthesis

The practical work involves independent, frontal, group, and interactive activity.

Assessment methods

– questioning

– analysis of clinical cases

– case studies

– tests

– summattive assessments

– individual work

– assessment of practical skills

– final exam

Teaching materials and resources used in seminars. To better acquire the knowledge about HL, different teaching materials are used, such as: tables, diagrams, algorithms, images, international guides. Power Point presentations and posters are used in seminars.

Questions for individual students` learning

1. Etiology and epidemiology of Hodgkin's lymphoma.

2. Pathogenesis of Hodgkin's lymphoma.
3. Clinical picture of Hodgkin's lymphoma.
4. International clinical classification of Hodgkin's lymphoma.
5. Diagnosis of Hodgkin's lymphoma.
6. Morphological classification of Hodgkin's lymphoma.
7. Laboratory tests for detection of Hodgkin's lymphoma.
8. Staging methods of Hodgkin's lymphoma
9. Differential diagnosis of Hodgkin's lymphoma.
10. Principles of treatment of patients with Hodgkin's lymphoma

Etiology of HL. There is currently a number of known factors that may contribute to the development of Hodgkin's lymphoma [8].

1. Ionizing irradiation
2. Genetic factors
3. Chemicals (aromatic hydrocarbon preparations such as benzene, toluene, insecticides and others.)
4. Viruses: Epstein-Barr (EBV), HIV, HTLV, HHV, etc.
5. Compromised immune system (immunosuppression): HIV/AIDS, patients after bone marrow transplantation, autoimmune diseases and others.).

Epidemiology HL. HL morbidity in the Republic of Moldova is equal to 1.47 per 100,000 inhabitants [8]. In the USA and the Russian Federation, HL morbidity is 2.8 and 2.2 per 100,000 population, respectively [9, 10]. In European countries it accounts for 2.2 - 3.58 per 100,000, in North Africa and the Middle East - 1.45 and in East Asia - 1.18 per 100,000 inhabitants [3, 16, 36]. HL can develop at any age, including children. The frequency of HL is higher in people aged 18-35 years, mostly 25-35 years [11, 15, 19, 25, 26, 28, 29]. The development of HL at a young age is commonly an important socio-economic problem [24]. The survival of patients with HL in local stages (I-II) with complete remissions of more than 10 years of NHL patients in local stages with complete remissions is greater than 90% [11, 13, 34]. Therefore, it is necessary to diagnose patients with HL in local stages (I and II) with a high recovery potential.

Pathogenesis. HL is a neoplastic process in the lymphoid tissue, which develops from B-lymphocytes marked by the appearance of Reed-Sternberg malignant cells in the association of a population of lymphocytes, histiocytes, and plasma cells. The unifocal (unicentric) theory is involved in the pathogenesis of HL. The spread of the malignant process from the initial primary focus takes place by the lymphatic route, and subsequently by the hematogenous one. Initially a single lymph node is involved, which gradually increases in size, then another lymph node is involved in the same area, later other lymph nodes are involved, forming the primary area. Thus, there is a sequence in the involvement of lymph nodes in the primary tumor area (lymph nodes are involved in turn). Subsequently, there is a sequence in the spread of the malignant process in other lymph nodes, usually in the areas adjacent to the primary one.

Clinical picture of Hodgkin's lymphoma

The clinical picture of HL depends on the location of the primary focus of the tumor and the degree of spread of the malignant process (clinical stage). In 97-98% of cases, the onset of HL occurs in the lymph nodes, mainly in the peripheral ones (80-85%). Swelling of the lymph nodes is one of the first signs of HL. Primary HL frequently develops in the cervical lymph nodes (50%), followed by the supraclavicular ones (25%). The cervical lymph nodes on the left are affected more often than those on the right. HL can have a primary development in the axillary lymph nodes up to 13%. There is rarely primary involvement of inguinal lymph nodes (1-3%). HL develops in the mediastinum and abdominal lymph nodes in 10% and up to 7.5%, respectively. In other groups of lymph nodes HL develops very rarely. The primary involvement of various organs and tissues occurs only in 1-2% of cases. Thus, in most cases the onset of HL in the peripheral lymph nodes, mainly the cervical ones, which are conspicuous, can help establish the diagnosis of the disease in the early stages with a high recovery potential.

In cases of involvement of the peripheral lymph nodes, only lymphadenopathy is revealed depending on the location of the malignant process. The affected lymph nodes are painless and do not adhere to

adjacent tissues. When HL develops in the mediastinum, as long as the lymph nodes are small, clinical signs are missing and only imaging tests can detect the enlargement of the lymph nodes. Usually dry cough, as well as signs of compression syndrome of the superior vena cava can occur along with the enlargement of the lymph nodes in the mediastinum. In cases of primary involvement of the abdominal lymph nodes, due to their small size, there are no clinical signs, and only ultrasonography and computed tomography of the abdomen can detect them. At the onset the clinical manifestations of HL in other organs and tissues, which occur very rarely, are the same as in cases of malignant tumors of these organs. At the generalized stage, any organ or tissue can be affected. There are commonly metastases in the liver (30-80%), spleen (65-80%), lung tissue (20-44.8%), bones (20-25%), bone marrow (10%) and others. The gastrointestinal tract is rarely involved. At the generalized stage of HL malignant process, symptoms of general intoxication may appear, such as fever, weight loss, and excessive sweating.

In rare cases, the first symptom of HL may be fever that is not specific. Fever can have a septic, undulant and remittent character. Itchy skin is rarely one of the first signs of HL. In both cases, if the peripheral lymph nodes are not involved, the patient should be examined very well to rule out the primary involvement of the mediastinal and abdominal lymph nodes or other organs and tissues. The signs of general intoxication indicate an unfavorable prognosis and aggressive evolution of the disease. Symptoms of general intoxication occur more frequently in the generalized stages of HL. Other unfavorable factors that influence negatively the evolution of HL are:

- Age > 50 years;
- Mediastinal-thoracic index > 0.35 (mediastinal shadow enlargement due to lymph nodes enlargement more than 1/3 of the rib cage diameter;
- Involvement of 4 and more lymph node areas;
- ESR > 50 mm/h or more than 30 mm/h in cases of intoxication symptoms.

The clinical picture of HL depends on the location of the primary focus and the degree of spread of the malignant process. To express the degree of spread of the malignant process, the International Clinical Classification was developed in Ann Arbor, USA, in 1971, which is still used today. According to the International Clinical Classification, there are 4 stages of HL.

International Clinical Classification of HL

Stage I. Involvement of a single lymph node area (I) or a single extranodal organ (I E).

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

Stage III. Involvement of two or more lymph node areas on both sides of the diaphragm (III) or localized primary involvement of an extranodal organ and two or more areas 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. 1*).

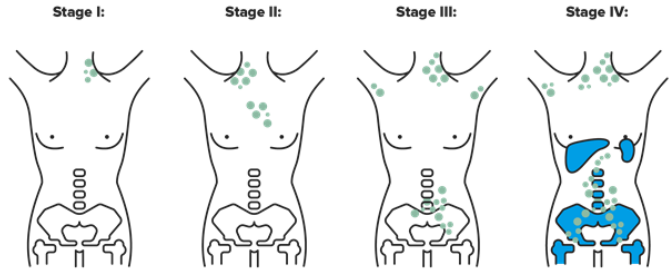

***Fig. 1*. Clinical stages of HL**

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

A - no symptoms of general intoxication

B - symptoms of general intoxication (*fig. 2.*).

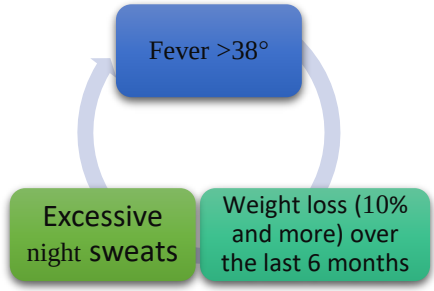

Fig. 2. **Signs of general intoxication.**

Only one of these signs will suffice to establish the presence of symptoms of general intoxication (B).

Depending on the presence of biological signs of the pathological process, each stage is divided into **a** (absence of biological signs of the pathological process) and **b** (presence of biological signs of the malignant process). The biological signs include:

a. ESR > 30 mm/hour

b. fibrinogen > 5.0 g/l

c. α-2 globulin > 10 g/l

d. ceruloplasmin > 0.4 Un

e. haptoglobin > 1.5 m

In order to determine the presence of biological signs (b), it is necessary reveal at least two of these signs.

The symptoms of general intoxication have prognostic significance, and the biological signs indicate the activity of the malignant process and are important for treatment and hospitalization**.**

Currently, research is focused on determining the prognostic factors for developing an optimal therapeutic tactics. Many scientific centers use different prognostic factors that influence the formation of prognostic groups [10]. The following prognostic groups were made to develop treatment tactics:

1. GHSG (German Hodgkins Lymfoma Study Group) (*tab.1*)
2. EORTC (European Organization for the Research and Treatment of Cancer) (*tab.2*)

3. NCIC/ECOG National Cancer Institute of Canada and Eastern Cooperative Oncology Group) (tab.3)

Table 1.

GHSG prognostic criteria

Prognostic groups	GHSG
Early stages, favorable prognosis	Stages I-II without risk factors
Early stages, unfavorable prognosis	Stages I-II, C or D - with risk factors, but A and B – with no risk factors.
Massive tumors	Stages I-II, A and B - with risk factors. Stages III-IV
Risk factors	A - massive mediastinum * B - Stage E C - increased ESR ** D - ≥ 3 lymph node areas

Note: GHSG - German Hodgkin`s Lymphoma Study Group.

* Massive mediastinal tumor - tumor size larger than 1/3 of the rib cage diameter on the anterior radiograph.

** ESR > 50 in stage A, ESR > 30 in stage B.

Table 2

EORTC / GELA prognosis criteria

Prognostic groups	EORTC/GELA
Early stages, favorable prognosis	Stages I-II, involvement above the diaphragm, without risk factors
Early stages, unfavorable prognosis	Stages I-II, involvement above the diaphragm, with one or more risk factors
Generalized stages	Stages III-IV
Risk factors	A - massive mediastinum * B - age ≥ 50 years C - increased ESR ** D - ≥ 4 lymph node areas

Note: EORTC/GELA - European Organization for the Research and Treatment of Cancer / Groupe d' Etude des Lymphomes del' Adult

* Massive mediastinal tumor - tumor size larger than 1/3 of the rib cage diameter on the previous radiograph.

** ESR > 50 in stage A, ESR > 30 in stage B.

Table 3

NCIC / ECOG prognosis criteria

Prognostic groups	NCIC/ECOG
Early stages, favorable prognosis	Involvement of a single lymph node Histological variant of lymphoid depletion and nodular sclerosis (size g/l not more than 3 cm)
Early stages, unfavorable prognosis	Massive involvement of the mediastinum Involvement of peripheral or intra-abdominal lymph nodes
Generalized stages	Stages III and IV
Risk factors	A - age > 50 years B - mixed cellularity variant or lymphoid depletion C - ESR > 50 mm / hour D - involvement of more than 4 lymph nodes.

Diagnosis of Hodgkin's Lymphoma

The diagnosis of HL is morphologically confirmed by cytological, histological, and immunohistochemical analysis of swollen lymph node biopsy. It is necessary to perform the biopsy of the lymph nodes inflamed for a long time, because in the lymph nodes inflamed for a short time, the typical structure of HL may not yet be formed. Biopsy of swollen lymph nodes is performed in surgery departments. In case of the onset of HL in the mediastinum and lack of peripheral lymph nodes, it is necessary to perform mediastinoscopy, mediastinotomy, or thoracotomy, to obtain material for morphological and immunohistochemical analysis, and laparatomy in patients with tumor localized only in the abdomen. The diagnosis is confirmed only in the presence of specific Reed-Sternberg or Berezovsky-Sternberg cells. These cells were described by Berezovsky S.Y. (1890), Paltauf (1897), Sternberg (1898), and Reed (1902). The origin of these cells was not known for a long time. They were supposed to come from the monocyte-macrophage-histiocyte line. Subsequently, with the development of immunohistochemical and cytogenetic methods, there are data confirming that Reed-Sternbeg cells in 80 % of cases come from B-lymphocytes and in 20 % from T-lymphocytes. But in recent years Reed-Sternberg cells are thought to be of B-cell origin only [10].

Cytological analysis is performed by examining the swollen lymph node biopsy or the biopsy of the removed lymph node samples. The Romanowsky-Giemsa staining is carried out. Cytological analysis is only relevant when HL is suspected. In order to confirm the diagnosis and the morphological variant of HL, histological and immunohistochemical analysis of the material obtained at the biopsy of swollen lymph nodes is mandatory. Immunohistochemical analysis is of particular importance, because Reed-Sternberg tumor cells have specific markers CD15 and CD30 on their surface. For the nodular form with lymphocyte predominance, CD20 is positive. The last morphological classification of Hodgkin's lymphoma was developed by the WHO in 2016, revised in 2017 [30, 31] (table 4).

Table 4.

Morphological classification of Hodgkin's lymphoma, WHO, 2017

Hodgkin's lymphoma	Variants	Immunophenotype of tumor substrate
Nodular lymphocyte-predominant HL		CD 20 $^{+}$, CD 45^{+}, CD 30^{-}, CD15- (in some cases positive expression), BCL-6 +/-, PU.1 +, y-chain +, BoB1 +, MUM.1/ +.
Classical form	• lymphocyte predominance • nodular sclerosis (type I and II) • mixed cellularity • lymphocyte depletion	CD 30 $^{+}$, CD 15^{+}, CD 20^{-}, CD45- , PAX5 (weak nuclear expression), BoB1 -, MUM.1 +.

The nodular lymphocyte-predominant HL constitutes up to 5 % of HL and is characterized by a slow progression.

There are 4 types of classical HL. The lymphocyte-predominant type develops in 5 % and is characterized by diffuse lymphocyte proliferation, sometimes in association with histiocytes, eosinophils or plasma cells. There are few Reed-Sternberg cells. Fibrosis and necrosis are absent.

The type of nodular sclerosis constitutes 60 % - 80 % of HL structure. This type of HL develops mainly in young people aged 15-35 with a predominance of women. It is characterized by bands of collagenic structure, which circumscribe the pathological tissue nodules in the

lymph nodes. There are Reed-Sternberg cells, lymphocytes, histiocytes, and eosinophils in these nodules. There are also lacunar Reed-Sternberg cells, which have a small monolobal nucleus and a poorly stained abundant cytoplasm. Nodular sclerosis was divided into type I and II according to the frequency of lacunar Reed-Sternberg cells. In type II nodular sclerosis, the percentage of lacunar Reed-Sternberg cells is higher and has a severe evolution.

Mixed cellularity HL develops in 15-30 % of cases. This type is characterized by a polymorphic cellularity of histiocytes, neutrophils, eosinophils, plasma cells and numerous Reed-Sternberg cells. There are foci of fibrosis and necrosis.

The type of lymphocyte depletion is rarely found and constitutes 5-10 %. It is characterized by a considerable decrease in lymphocytes until their complete absence and the presence of many Reed-Sternberg cells. This type of HL has an aggressive evolution and a reserved prognosis.

Laboratory tests in Hodgkin's lymphoma

The complete peripheral blood count is with no specific changes. In some cases, lymphopenia, monocytosis, and eosinophilia may occur, which are very rare. Increased ESR reflects the activity of the malignant process. In cases of bone marrow involvement, anemia, leukopenia, and thrombocytopenia can occur. These changes are not specific and do not help establish the diagnosis. To confirm or exclude bone marrow metastases, it is necessary to perform trepanobiopsy of the iliac bone. The biochemical tests that reflect the activity of the malignant process are the increased levels of fibrinogen, α-2 globulins, ceruloplasmin and haptoglobin.

Methods of Hodgkin's lymphoma staging

To determine the degree of spread of the malignant process (clinical stage), it is necessary to carry out:

1. **Clinical examination** of the patient which includes palpation of all peripheral lymph nodes, liver and spleen, determination of the presence of symptoms of general intoxication B (fever > 38°, night sweats, weight loss).

2. **Laboratory tests:** complete peripheral blood count, ESR, fibrinogen, haptoglobin, ceruloplsmin, α-2 globulin, LDH, alkaline

phosphatase, biochemical tests to determine the renal and hepatic function, glucose, uric acid and others.

3. **Imaging tests**: chest X-ray with mediastinal tomography, abdominal ultrasound, nasopharyngeal tomography, computed tomography of the neck, chest, abdomen and pelvis; positron emission tomography (PET / CT).

4. **Endoscopy if necessary** - fibroepipharyngoscopy, fibrogastroduodenoscopy and fibrocolonoscopy.

5. **Bone scintigraphy and radiography as needed (bone pain).**

6. **Trepanobiopsy** of the iliac bone with histological examination of the bone marrow.

Differential diagnosis of HL

The differential diagnosis of HL needs to be made between HL and the following conditions:

- Non-Hodgkin's lymphoma
- Lymph node involvement in leukemia
- Lymph nodes metastases
- Tuberculous lymphadenitis
- Reactive lymph node hyperplasia

Non-Hodgkin's lymphoma (NHL) as opposed to commonly (42-45 %) primary HL develops extranodally (Waldeyer's lymph ring, gastrointestinal tract, spleen, etc.) with the clinical picture of the tumor formation. In cases of NHL development in the peripheral lymph nodes, the consecutive appearance of the lymph nodes in the primary focus is also characteristic, but often there is no consecutive spread of the malignant process in other areas of the lymph nodes. In NHL, bone marrow is frequently affected. Bone marrow involvement in indolent NHL occurs in 60-65 % of cases, and in 20-25 % of patients in aggressive forms. In cases of indolent NHL with bone marrow involvement and leukemia, in complete analysis of blood and bone marrow the percentage of lymphocytes will increase and prolymphocytes will also be present. In aggressive NHL with leukemia of both bone marrow and peripheral blood, blast cells will be present. The definitive diagnosis can be established only by morphological and immunohistochemical analysis of the lymph node biopsy.

Lymph node involvement in leukemia. One of the clinical manifestations of leukemias (acute leukemia, chronic lymphocytic leukemia, chronic monocytic leukemia, etc.) is lymphadenopathy. For the diagnosis of lymphadenopathy that develops in patients with leukemia, the examination of the general analysis of the peripheral blood and bone marrow, in which the morphological substrate of leukemia is detected, is of significant importance. In acute leukemia the blast cells are the morphological substrate, while in chronic lymphocytic leukemia - lymphocytes, and in chronic monocytic leukemia - monocytes. Thus, in the differential diagnosis of HL with lymph node involvement in leukemia, the decisive role is played by specific changes in the general analysis of peripheral blood and bone marrow.

Cancer metastases in lymph nodes. Cancer metastases show the dissemination of the malignant process in lymph nodes in the primary focus of the tumor. In patients with metastases along with swollen lymph nodes, in most cases there are also clinical manifestations of the tumor of the organ or tissue in which cancer developed. Lymph nodes in cancer metastases are usually hard in consistency. However only the physical properties of the lymph nodes do not help establish the diagnosis. To confirm the diagnosis it is necessary to perform lymph node biopsy along with the morphological and immunohistochemical analysis.

Tuberculous lymphadenitis. In tuberculous lymphadenitis, one or more areas of lymph nodes are affected. The diagnosis can be made only as a result of cytological and histological analysis of swollen lymph nodes.

Reactive lymph node hyperplasia. Reactive lymph node hyperplasia manifests as a regional reaction of the lymph nodes in the presence of a focus of infection targeting the skin, tunica mucosa, palatine tonsils, teeth, acute respiratory viral infections, etc. Reactive lymph node hyperplasia is the most common form of benign lymphadenopathy. In reactive hyperplasia as opposed to HL, there is a lack of sequential order in the appearance of lymph nodes and the consecutive spread in other areas of lymph nodes. The lymph nodes enlarge simultaneously in a certain region or in several anatomical areas and are of the same size. It is not the primary affected area. If it is a

single lymph node, it does not increase in size. In cases of reactive hyperplasia, subsequently the size of the lymph nodes decreases.

Principles of treatment of Hodgkin's lymphoma

The goal of treatment is to completely cure patients with HL, especially in the local stages (I-II). HL is one of the first oncological diseases with a high recovery potential. Currently, due to the implementation of intensive polychemotherapy (PChT) in combination with radiotherapy (RT), the survival of over 5 and 10 years of HL patients reached 87 % and 81 %, respectively [32, 33]. In the local stages, the survival of more than 5 and 10 years exceeds 90 % [19, 34]. The effectiveness of the first-line treatment is high, in the local stages (I-II) complete remission constitutes 90-95 % [1, 4, 12, 14].

1. Chemotherapy involves the administration of chemotherapeutic agents which have an important role in the destruction of tumor cells. These substances have adverse reactions with a different degree of severity depending on the patient and the type of treatment used. The most common short-term reactions are nausea, vomiting, hair loss. Long-term reactions include infertility, lung and heart involvement, other malignant tumors.

Various polychemotherapy regimens are used for the treatment of Hodgkin's lymphoma, among which the most common are: ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine), BEACOPP (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone).

2. Radiotherapy involves gamma ray or X-ray irradiation to destroy a tumor mass and is used mainly in the local stages (I-II), usually in combination with chemotherapy (not simultaneously).

3. Immunotherapy involves using the immune system to fight tumor cells. Monoclonal antibodies are used (Brentuximab vedotin - anti-CD30 antibody, Rituximab - anti-CD20 antibody), or more recently „checkpoint inhibitors” (Nivolumab - anti-PD 1 antibody, Pembrolizumab - anti-PD 1 receptor antibody).

The treatment of Hodgkin's lymphoma should be individualized and involves the use of one or more methods, being adjusted according to the

stage of the disease, its prognosis, and the functional status of the patient.

In localized stages (I-II), 2-4 cycles of PChT are administered. After cycle 2 of PChT, PET/CT is performed. In cases of negative PET/CT, 1 more cycle of PChT + RT to the affected areas, are carried out. In patients with positive PET / CT, another 2 cycles of an more intensive PChT regimen are administered after which RT is applied to the affected areas. RT (2 Gy) is performed daily, 5 days a week, a total of 30 Gy being applied.

In the localized stages of HL(I-II) with an unfavorable prognosis (intermediate stages), the same combined way of treatment is applied (chemotherapy + RT), but with the intensification of the PChT regimens.

In generalized stages III-IV, 6-8 cycles of PChT are administered as needed. PET/CT is performed after 4 cycles of PChT to assess treatment effectiveness. RT is only applied to residual foci (*fig. 3*).

In localized stages with a favorable prognosis, the treatment with PChT is performed according to the ABVD scheme (tab.5). In generalized stages with an unfavorable prognosis, the therapy with the BEACOPP- escalated regimen is initiated (*tab.6*). Currently, there is a tendency to intensify the first-line

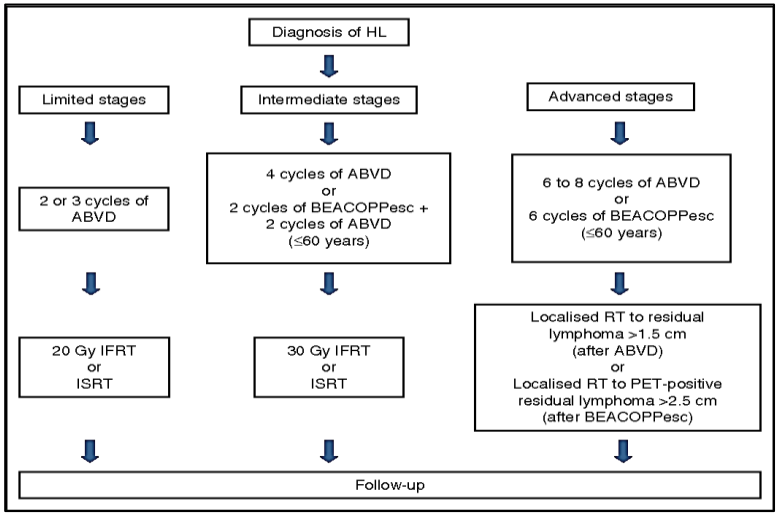

Fig. 3. The treatment algorithm of patients with HL.

**IFRT – Involved field radiation therapy; ** ISRT - Involved site radiation therapy.*

PChT regimens in order to achieve a qualitative and complete remission. The use of PET / CT which evaluates treatment efficacy contributes significantly to the subsequent tactics of HL therapy [20].

Table 5

ABVD PChT regimen

Drug	***Dose mg/m²***	***Days of administration***
Adriamycin	25 mg/m² i.v.	Days 1 + 15
Bleomycin	10 mg/m² i.v.	Days 1 + 15
Vinblastine	6 mg/m² i.v.	Days 1 + 15
Dacarbazine	375 mg/m² i.v.	Days 1 + 15

Resumption of cycle: day 29.

Table 6

BEACOPP – escalated PChT regimen

Drug	**Dose mg/m²**	**Days of administration**
Bleomycin	10 mg/m² i.v.	Day 8
Etoposide	200 mg/m² i.v.	Days 1–3
Adriamycin	35 mg/m² i.v.	Day 1
Cyclophosphamide	1250 mg/m² i.v.	Day1
Vinblastine	1,4 mg/m², max 2 mg i.v.	Day 8
Procarbazine	100 mg/m² p.o.	Days 1–7
Prednisone	40 mg/m² p.o.	Days 1–14
G-CSF	s.c.	From the 8th day

Resumption of cycle: day 22.

Complete remission is considered in cases of complete tumors resorption, confirmed by PET/CT. If it is not possible to perform PET/CT, CT of the chest, abdomen, and pelvis should be performed. A decrease in tumor size of more than 50% is considered partial remission. Tumor shrinkage less than 50 % or tumor progression accounts for lack of remission.

Although the effectiveness of the first-line treatment is high, sooner or later relapses occur in 10-15% [2, 21, 24].

In cases of refraction and relapse, high-dose chemotherapy may be applied followed by hematopoietic stem cell autotransplantation or

allotransplantation (autotransplantation using HSC, allotransplantation using identical related or unrelated HLA donor HSC). Salvage regimens, for example DHAP (dexamethasone, high-dose ara-C, cisplatin), IGEV (ifosfamide, gemcitabine, vinorelbine, dexamethasone), or ICE (ifosfamide, carboplatin, etoposide) are administered to reduce tumor mass and mobilize stem cells prior to high-dose chemotherapy and ASCT [22, 27]. In some patients with relapse after the first-line treatment with two cycles of chemotherapy followed by radiotherapy, rescue therapy may be successfully administered with a second, more intensive, conventional chemotherapy regimen, e.g. BEACOPP - *escalated* [17].

In some patients with delayed localized recurrence, rescue radiotherapy without chemotherapy may be considered. In cases where complete remission is not achieved after the second-line treatment, brentuximab vedotin monotherapy (ant-CD30) may be used. The use of brituximab in combination with chemotherapy regimens at the cytoreduction stage prior to ASCT is currently being considered [7]. In patients at risk of developing relapses after ASCT, treatment with brentuximab vedotin alone in up to 16 strengthening treatments is indicated. Patients with relapses after ASCT and brentuximab therapy or patients who cannot be candidates for ASCT with relapses after brentuximab are recommended to use PD-1 inhibitors (nivolumab, pembrolizumab) alone [2, 21].

NLPHL treatment. Stage IA without risk factors. A 30 Gy summary dose of RT is the standard treatment for patients with stage IA NLPHL with no risk factors. In other stages, NLPHL is treated identically with HLc in all stages, except for stage IA without risk factors (23).

Patients with NLPHL relapse

Unlike most cases of HLc, NLPHL malignant cells are characterized by a strong CD20 expression. Therefore, localized relapses of NLPHL can be effectively treated with rituximab monotherapy. Patients with advanced relapses require a combination of rituximab with ABVD PChT [6].

Prognosis. Due to modern therapeutic strategies, permanent complete remissions are achieved in 80-90% of patients, who can be considered cured.

Monitoring. History, physical examination and laboratory tests (complete blood count, ESR and serum biochemistry tests) should be performed every 3 months for 2 years, then every 6 months up to 5 years, then once a year.

Clinical case

Patient M., 32 years old, complained of the presence of a tumor in the right cervical region.

The patient was ill for 2 months, when he first noticed a painless tumor in the right cervical region. In a month, new tumors appeared in the same region, which grew in size. He saw the family doctor and was diagnosed with lymphadenitis. Antibacterial treatment was indicated which had no effect, after which the patient was referred to the hematologist.

Objective: Clear skin. Palpation revealed enlarged lymph nodes, ranging in size from 1.5 to 3 cm, in the cervical region on the right, having an elastic consistency. Complete blood count: Hb-130 g / l, erythrocytes - $4.2 \cdot 10^{12}$/l, platelets - $336.0 \cdot 10^{9}$/l (80 ‰), leucocytes-$5.2 \cdot 10^{9}$/l, band neutrophils 4 %, segmented neutrophils 62%, eosinophils – 3 %, monocytes 8 %, lymphocytes 23 %, ESR-38 mm / hour, painless. Other groups of lymph nodes, spleen and liver - not palpable.

1. What is the presumptive diagnosis?
2. What is the diagnostic plan to make the definitive diagnosis?
3. What is the treatment tactics?

Clinical case

Patient B., 28, had no complaints. Rdiological examination (micro-rentgenography) found a tumor in the mediastinum. The patient was referred to the hematologist.

Objective: Clear skin. Hemorrhagic syndrome was missing, peripheral lymph nodes - not palpable; vesicular murmur in the lungs; clear heart sounds. Palpation revealed soft and painless abdomen; spleen and liver - not palpable.

Radiological examination - enlargement of the mediastinal lymph nodes (mediastinal shadow at tracheal bifurcation - 9.5 cm). (*fig, 4*)

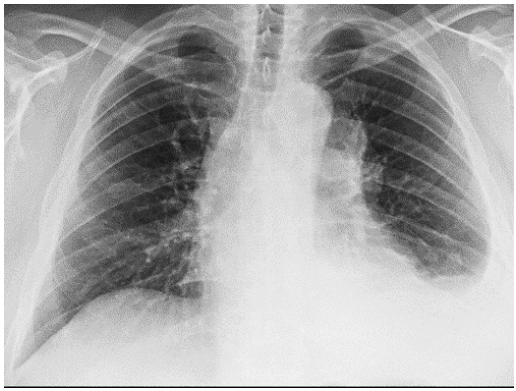

Fig. 4. **Postero-anterior pulmonary radiography of the patient.**

Complete blood count: Hb-120 g/l, er.-$4.0 \cdot 10^{12}$/l, leuc.-$6.0 \cdot 10^{9}$ / l, platelets - $280.0 \cdot 10^{9}$/l (70 ‰), band neutrophils 5%, segmented neutrophils 64%, eosinophils 4%, monocytes 7%, lymphocytes 20%, ESR-35 mm / hour.

1. What is the presumptive diagnosis?
2. What is the diagnostic plan to establish the definitive diagnosis?
3. What is the treatment tactics?

Assessment tests

S.C. The onset of Hodgkin's lymphoma occurs more frequently in:

A. Waldeyer`s lymphatic ring
B. Peripheral lymph nodes
C. Gastrointestinal tract
D. Spleen
E. Lung tissue

S.C. The clinical picture of Hodgkin's lymphoma depends on:

A. Complete blood count
B. Myelogram
C. Age
D. Location of the primary focus and the degree of spread of the malignant process
E. Serum biochemistry tests

S.C. An important criterion for Hodgkin's lymphoma is:

A. Presence of anemic syndrome
B. Concomitant enlargement of lymph nodes
C. Consecutive enlargement of lymph nodes
D. Presence of fever
E. Presence of hemorrhagic syndrome

S.C Definitive diagnosis of Hodgkin's lymphoma is made after:

A. Bone marrow aspiration
B. Morphological and immunohistochemical examination of the removed tumor
C. Hemogram
D. Serum biochemistry tests
E. Radiological examination

S.C. Hodgkin's lymphoma commonly involves the following lymph nodes:

A. Cervical

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

S.C. Morphological diagnosis of Hodgkin's lymphoma is confirmed by the presence in histological samples of:

A. Plasma cells
B. Lymphocytes
C. Blast cells
D. Reed-Sternbeg cells
E. Prolymphocytes

S.C. Specific changes in hemogram in Hodgkin's lymphoma are:

A. Lymphocytosis
B. Thrombocytopenia
C. Leukopenia
D. Leukocytosis
E. absent

S.C. In the treatment of Hodgkin's lymphoma, localized stages (I-II), with a favorable prognosis, should be applied:

A. 2-4 cycles of polychemotherapy + radiotherapy (summary dose - 30 Gy) in the affected areas
B. Monochemotherapy
C. Surgical treatment
D. Syndrome-based treatment
E. Radiotherapy

S.C. In the treatment of Hodgkin's lymphoma, generalized stages (III-IV), should be applied:

A. Monochemotherapy
B. Radiotherapy
C. Surgical treatment

D. Polychemotherapy (6-8 cycles) with radiotherapy in the residual areas

E. Surgical treatment + radiotherapy

S.C. As a result of tests performed, it was found that the patient`s cervical lymph nodes were swollen bilaterally, but mediastinal lymph nodes were without signs of general intoxication. Determine the clinical stage of Hodgkin's lymphoma:

A. I A

B. II A

C. II B

D. III A

E. IV A

S.C. Examination of a patient with Hodgkin's lymphoma revealed the enlargement of cervical lymph nodes, bilateral enlargement of axillary lymph nodes, mediastinal and abdominal ones, as well as fever was determined. Determine the clinical stage:

A. I A

B. II B

C. III A

D. III B

E. IV B

S.C. The diagnosis of mediastinal Hodgkin's lymphoma is confirmed by:

A. Hemogram

B. Thoracotomy or mediastinoscopy with morphological and immunohistochemical analysis of the mediastinal tumor

C. Radiological examination

D. Computed tomography

E. Bone marrow aspiration

S.C. In case of lymphadenopathy and if Hodgkin's lymphoma is suspected, the most important test is:

A. Computed tomography
B. PET / CT
C. Chest X-ray
D. Lymph node biopsy
E. Ultrasound examination

M.C. Hodgkin's lymphoma is characterized by:

A. Consecutive appearance of lymph nodes in the primary area
B. Frequent extranodal onset
C. Consecutive spread of the malignanat process in lymph nodes
D. Hemorrhagic syndrome
E. Anemic syndrome

M.C. The following statements are correct for Hodgkin's lymphoma:

A. The onset commonly occurs in the Waldeyer`s lymph ring
B. The onset commonly occurs in peripheral lymph nodes
C. Consecutive enlargement of lymph nodes
D. The onset commonly occurs in the gastrointestinal tract
E. Concomitant enlargement of lymph nodes

M.C. In Hodgkin's lymphoma, the presence of general intoxication signs involves:

A. Favorable prognosis
B. Favorable evolution of the disease
C. Aggressive evolution of the disease
D. Unfavorable prognosis
E. High efficacy of the treatment

M.C. The following statements are correct for Hodgkin's lymphoma:

A. Symptoms of general intoxication have no prognostic significance
B. Symptoms of general intoxication are of prognostic significance

C. The morphological type has no prognostic significance
D. The morphological type is of prognostic importance
E. Computed tomography definitively confirms the diagnosis

M.C. The following statements are correct for the treatment of Hodgkin's lymphoma:

A. In generalized stages (III-IV) only radiotherapy is applied
B. Development of the treatment method depends on the clinical stage
C. In localized stages (I-II), monochemotherapy is the treatment of choice
D. In generalized stages (III-IV), polychemotherapy is used, while radiotherapy in residual foci
E. In stage I, specific treatment is not indicated

M.C. In cases of bone marrow involvement in Hodgkin's lymphoma in complete blood count can be revealed:

A. Leukopenia
B. Anemia
C. Erythrocytosis
D. Hyperthrombocytosis
E. Thrombocytopenia

M.C. In Hodgkin's lymphoma the intoxication symptoms are:

A. Fever
B. General weakness
C. Excessive night sweats
D. Weight loss more than 10% over the last 6 months
E. Bone pain

M.C. The biological signs of the pathological process in Hodgkin's lymphoma are:

A. ESR > 30 mm / hour
B. Increased bilirubin
C. Increased prothrombin

D. Fibrinogen > 5.0 g / l
E. Haptoglobin > 1.5%

M.C. Factors that influence negatively the prognosis of Hodgkin's lymphoma are:

A. Involvement of 1-2 lymph node areas
B. Involvement of 4 or more lymph node areas
C. Age > 50 years
D. Enlargement of mediastinal shadow due to enlargement of lymph nodes more than 1/3 of the rib cage diameter (mediastinal-thoracic index > 0.35)
E. High efficacy of treatment

M.C. The morphological types of classical Hodgkin's lymphoma are:

A. Lymphoblastic
B. Nodular sclerosis
C. Mixed cellularity
D. Lymphocytic type containing small lymphocytes
E. Lymphocyte depletion

M.C. The following statements are correct for Hodgkin's lymphoma:

A.The onset of Hodgkin's lymphoma commonly occurs in lymph nodes
B. It commonly has a primary extranodal development
C. It never affects the bone marrow
D. It frequently develops in people aged 25-35 years
E. Extranodal onset is very rare

M.C. For nodular lymphocyte-predominant Hodgkin's lymphoma, the following statements are correct:

A. Aggressive evolution
B. Favorable evolution
C. Positive CD20
D. Involvement of the central nervous system occurs frequently
E. The frequency is 5%

M.C. In order to stage Hodgkin's lymphoma, the following tests are performed:

A. Computed tomography
B. PET / CT
C. Ultrasound examination
D. Trepanobiopsy
E. Sternal puncture

M.C. The morphological types of classical Hodgkin's lymphoma are:

A. Lymphocyte predominance
B. Nodular sclerosis
C. Mixed cellularity
D. Lymphoplasmacytic
E. Lymphocyte depletion

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