

**KHARKIV NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF INTERNAL MEDICINE N3**

METHODOLOGICAL RECOMMENDATIONS FOR STUDENTS

“Lymphomas and multiple myeloma”

Kharkiv 2012

Module 4. “The basic foundations of diagnostics, treatment and prophylaxis of common hematological diseases”.

Practical lesson N 28 “Lymphomas and multiple myeloma”

Topicality

The incidence of Hodgkin's lymphoma varies substantially around the world. The highest rates occur in the United States, Canada, Switzerland, and northern Europe. Intermediate rates are seen in southern and eastern Europe and low rates in eastern Asia. No clear explanation for this variation in incidence has been found.

Incidence is approximately 4 new cases/100 000 population/year. Sex ratio: slight male excess (1.5:1). Median age is 31 years; first peak at 20-35 years and second at 50-70 years. The incidence of Hodgkin's lymphoma rises from a very low level in childhood to a plateau in early adulthood and then remains stable.

Geographic differences in the incidence of non-Hodgkin's lymphomas vary as much as five-fold. The highest rates are seen in the United States, Europe, and Australia, whereas lower rates are seen in Asia. Incidence is approximately 12 new cases/100 000 people/year. Sex ratio: slight male excess. Median age is 65-70 years.

Multiple myeloma accounts for 1% of all malignant disease and slightly more than 10% of hematologic malignancies. The annual incidence of multiple myeloma is 4 per 100,000. An apparent increased incidence in recent years is probably related to increased availability and use of medical facilities, especially for older persons. Multiple myeloma occurs in all races and all geographic locations. Its incidence in blacks is almost twice that in whites. Multiple myeloma is slightly more common in men than in women. The median age of patients at the time of diagnosis is about 65 years; only 2% of patients are younger than 40.

Educational goals:

- To give definition of lymphomas and multiple myeloma;
- To become familiar with etiology and pathogenesis of different types of lymphomas and multiple myeloma;
- To become acquainted with modern classifications of lymphomas and multiple myeloma;
- To learn methods of investigations of hematological malignancies with special emphasis on indications and contraindications to them;
- To learn how to interpret data of laboratory and instrumental investigations;
- To study how to manage lymphomas and multiple myeloma.

What student should know?

- The basic etiologic factors and pathogenetic mechanisms of lymphomas and multiple myeloma development;
- The basic clinical syndromes of lymphomas and multiple myeloma;
- The chief complaints and physical finding in lymphomas and multiple myeloma;
- The methods of physical examination of patients with lymphomas and multiple myeloma;
- The diagnostic value of clinical blood analysis in lymphomas and multiple myeloma;
- The diagnostic meaning of lymph node biopsy, indications and contraindications for this procedure;
- The list of instrumental investigations, which allow to identify splenomegaly, hepatomegaly, enlargement of intrinsic lymph nodes, malignant infiltration of different organs;
- The complications of lymphomas and multiple myeloma;
- The particularities of management of patients with lymphomas and multiple myeloma;
- The particularities of treatment of lymphomas and multiple myeloma (curative regimen, chemotherapy, supportive care, radiotherapy, bone marrow transplantation);
- The prophylaxis of the lymphomas and multiple myeloma.

What student should know how to do?

- the identification of main clinical syndromes in lymphomas and multiple myeloma;
- the development of treatment plan of patients with lymphomas and multiple myeloma;
- the interpretation of laboratory findings in case of lymphomas and multiple myeloma;
- the clarification of differential diagnosis;
- the drugs prescription to patients with lymphomas and multiple myeloma;
- the evaluation of prognosis of acute and chronic lymphomas and multiple myeloma

Practical skills:

- Inspection of skin, its derivatives and visible mucous membranes;
- Palpation of peripheral lymph nodes;
- Inspection of abdomen;
- Superficial palpation of abdomen;
- Deep sliding palpation of abdomen;
- Percussion of liver and spleen.

LYMPHOMAS

These neoplasms arise from lymphoid tissues, and are diagnosed from the pathological findings on biopsy as Hodgkin or non-Hodgkin lymphoma. The majority are of B- cell origin. Non-Hodgkin lymphomas are classified as low- or high-grade tumours on the basis of their proliferation rate. High-grade tumours are dividing rapidly, have only been present for a matter of weeks before diagnosis and may be life-threatening. Low-grade tumours are dividing slowly, may have been present for many months before diagnosis and behave in an indolent fashion.

HODGKIN LYMPHOMA

Hodgkin's lymphoma, formerly called Hodgkin's disease, is one of the B-cell lymphomas. It has a characteristic neoplastic cell, the Reed-Sternberg cell, a distinct natural history, and most importantly, an excellent response to treatment, with the large majority of patients being cured.

ETIOLOGY

The cause of Hodgkin's lymphoma remains unclear. Hodgkin's lymphoma is not associated with exposure to radiation, chemicals, biocidal agents, working in health care-related professions, or previous tonsillectomy. More common in patients from well-educated backgrounds and small families. Three times more likely with a past history of infectious mononucleosis but no causal link to Epstein-Barr virus infection proven.

WHO PATHOLOGICAL CLASSIFICATION AND INCIDENCE OF HODGKIN LYMPHOMA (HL)

Hodgkin's lymphoma can typically be classified into one of five well-described subtypes. Reproducibility of the distinctions among these subtypes has been confirmed in the current widely accepted World Health Organization classification of lymphoid neoplasms. With addition of the new category of lymphocyte-rich classic Hodgkin's lymphoma, this newest classification scheme permits confident identification of nodular lymphocyte-predominant Hodgkin's lymphoma as a separate entity. The most common subtype is nodular sclerosing, which has characteristic course bands of sclerosis surrounding nodules composed of typical Reed-Sternberg cells in the usual background mixture of reactive and inflammatory cells.

Type	Histology	Incidence
Nodular lymphocyte- predominant HL		5%
Classical HL	Nodular sclerosing	70%
	Mixed cellularity	20%
	Lymphocyte-rich	5%
	Lymphocyte-depleted	Rare

The histological hallmark of Hodgkin lymphoma (HL) is the presence of Reed-Sternberg cells, which are large malignant lymphoid cells of B-cell origin. They are often only present in small numbers but are surrounded by large numbers of reactive normal T cells, plasma cells and eosinophils. The WHO classification is based on histology. Nodular lymphocyte-predominant HL is slow-growing, localised and rarely fatal. Classical HL is divided into four histological subtypes from the appearance of the Reed-Sternberg cells and surrounding reactive cells. The nodular sclerosing type accounts for the initial peak in young patients and is more common in women. Mixed cellularity is more common in the elderly peak. Lymphocyte-rich HL usually presents in men. Lymphocyte-depleted HL is rare and probably represents large cell or anaplastic non-Hodgkin lymphoma. **Clinical features** Hodgkin's lymphoma is usually manifested as lymphadenopathy typically in the cervical, axillary, or mediastinal areas, and only about 10% of the time as nodal disease below the diaphragm. Although peripherally located nodes seldom reach large size, very large mediastinal masses or, less often, retroperitoneal masses can develop with only modest symptoms. Lymph node involvement in Hodgkin's lymphoma is usually painless, but an occasional patient notes discomfort in involved nodal sites immediately after drinking alcohol.

Approximately 25% of patients with Hodgkin's lymphoma have constitutional symptoms. The classic B symptoms, significant weight loss (>10% of baseline), night sweats, or persistent fever, usually signal widespread or locally extensive disease and imply a need for systemic treatment. Generalized pruritus, occasionally severe, can antedate the diagnosis of Hodgkin's lymphoma by up to several years. Some patients have symptoms suggestive of a growing mass lesion, such as cough or stridor as a result of tracheobronchial compression from mediastinal disease or bone pain secondary to metastatic involvement. Because Hodgkin's lymphoma can involve the bone marrow extensively, an occasional patient has symptomatic anemia or incidentally noted pancytopenia. Paraneoplastic neurologic or endocrine syndromes have been reported with Hodgkin's lymphoma but are rare.

Investigations Treatment of HL depends upon the stage at presentation; therefore investigations aim not only to diagnose lymphoma but also to determine the extent of disease

CLINICAL STAGES OF HODGKIN LYMPHOMA (ANN ARBOR CLASSIFICATION)

Stage	Definition
I	Involvement of a single lymph node region (I) or extralymphatic site (I _E)
II	Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side of (above or below) the diaphragm (II _E)

III	Involvement of lymph node regions on both sides of the diaphragm with (III _E) or without (III) localised extralymphatic involvement or involvement of the spleen (III _S) or both (III _{SE})
IV	Diffuse involvement of one or more extralymphatic tissues, e.g. liver or bone marrow
A	No systemic symptoms
B	Weight loss, drenching sweats
The lymphatic structures are defined as the lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches.	

Diagnosis The diagnosis of Hodgkin's lymphoma is based on recognition of Reed-Sternberg cells or Hodgkin's cells (or both) in an appropriate cellular background in tissue sections from a lymph node or extralymphatic organ, such as bone marrow, lung, or bone. Fine-needle aspiration biopsy is not adequate for the diagnosis of Hodgkin's lymphoma. Open biopsy and standard histochemical staining are required to establish the diagnosis unequivocally and to determine the histologic subtype. *Full blood count* may be completely normal. A normochromic, normocytic anaemia may be present and, together with lymphopenia, is a bad prognostic factor. An eosinophilia or a neutrophilia may be present.

- *ESR* may be raised.
- *Renal function tests* are required to ensure function is normal prior to treatment.
- *Liver function* may be abnormal in the absence of disease or reflect hepatic infiltration. An obstructive pattern may be caused by nodes at the porta hepatis.
- *LDH measurements*, as raised levels are an adverse prognostic factor.
- *Chest X-ray* may show a mediastinal mass.
- *CT scan* of chest and abdomen to permit staging. Bulky disease (greater than 10 cm in a single node mass) is an adverse prognostic feature.
- *Lymph node biopsy* may be undertaken surgically or by percutaneous needle biopsy under radiological guidance.

Differential Diagnosis

Depending on the site of occurrence and associated symptoms, the differential diagnosis of Hodgkin's lymphoma includes non-Hodgkin's lymphoma, germ cell tumors, thymoma, sarcoidosis, and tuberculosis. However, the specific diagnosis is readily determined by obtaining an adequate biopsy specimen for review by an experienced hematopathologist. Proceeding to such a biopsy early in the assessment of patients with lymphadenopathy, especially of the mediastinum, often saves time and spares the patient needless testing and delay in diagnosis.

With the widespread availability of computed tomography (CT) and appropriate biopsy procedures to investigate enlarged central thoracic or intra-abdominal lymph nodes, the diagnosis of Hodgkin's lymphoma seldom presents difficulty. The immunophenotype can also help distinguish Hodgkin's lymphoma from other diseases.

Management

Treatment options include radiotherapy, chemotherapy or a combination of the two.

Radiotherapy Good results are obtained in localized stage IA or stage IIA disease with no adverse prognostic features. Careful planning is required to limit the doses delivered to normal tissues. Fertility is usually preserved after radiotherapy.

Women receiving breast irradiation during the treatment of chest disease have an increased risk of breast cancer and should be placed on a screening programme.

Patients continuing to smoke after lung irradiation are at particular risk of lung cancer.

Indications for radiotherapy

- Stage I disease
- Stage IIA disease with three or fewer areas involved
- After chemotherapy to sites where there was originally bulk disease
- To lesions causing serious pressure problems

Indications for chemotherapy

- All patients with B symptoms
- Stage II disease with more than three areas involved
- Stages III and IV disease

Chemotherapy

THE CHIVPP REGIMEN FOR HODGKIN LYMPHOMA

Drug	Dose
Chlorambucil	6 mg/m ² (up to 10 mg total) days 1-14 orally
Vinblastine	6 mg/m ² (up to 10 mg total) days 1 and 8 i.v.
Procarbazine	100 mg/m ² days 1-14 orally
Prednisolone	40 mg/m ² days 1-14 orally

All other patients are treated initially with chemotherapy. Over 80% of patients will respond to this combination therapy, with drugs delivered on an outpatient basis every 3-4 weeks for a total of 6-8 cycles. Treatment response is assessed clinically and by repeat CT.

This type of chemotherapy carries a high risk of inducing permanent infertility in men; adequate counselling and sperm storage must be offered at diagnosis. The risk of infertility is lower for women but advice about obtaining ovarian tissue before starting treatment should be given as appropriate. Premature menopause may result from treatment and hormone replacement therapy should be discussed with the patient. Corticosteroids can cause avascular necrosis of bone, particularly the femoral head. Myelodysplasia and acute leukaemia can occur 5-10 years after alkylating therapy but the incidence is less than 5%.

Combined modality therapy Radiotherapy may be given to the original sites of bulky disease after treatment by chemotherapy to reduce the risk of relapse. This form of treatment carries the greatest risk of long-term complications.

Prognosis Over 90% of patients with stage IA disease are cured by radiotherapy alone. Patients with stage IIA disease have a reduced cure rate from radiotherapy. Approximately 70% of patients treated with chemotherapy are cured. The 15% of patients who fail to respond to initial chemotherapy have a poor prognosis but some may achieve long-term survival after high-dose chemotherapy and autologous stem cell rescue. Patients relapsing after local radiotherapy have a good cure rate after subsequent chemotherapy but with an increased risk of long-term toxicity. Those relapsing within a year of initial chemotherapy have a good salvage rate with high-dose therapy and autologous stem cell rescue. Patients relapsing after 1 year may obtain long-term survival with further chemotherapy. **NON-HODGKIN LYMPHOMA** Non-Hodgkin lymphoma (NHL) represents a monoclonal proliferation of lymphoid cells and may be of B-cell (70%) or T-cell (30%) origin.

ETIOLOGY For most cases of non-Hodgkin's lymphoma, the etiology is unknown, although genetic, environmental, and infectious agents have been implicated.

Inherited disorders

Severe combined immunodeficiency disease

Common variable immunodeficiency disease

Wiskott-Aldrich syndrome

Ataxia-telangiectasia

X-linked lymphoproliferative disorder

Acquired disorders

Solid organ transplantation

Acquired immunodeficiency syndrome

Methotrexate therapy for autoimmune disorders

Rheumatoid arthritis

Sjögren's syndrome

Hashimoto's thyroiditis

Infectious agents

Epstein-Barr virus

Human T-cell lymphotropic virus type I

Human herpesvirus 8

Hepatitis C virus

Helicobacter pylori

Borrelia burgdorferi

Chlamydia psittaci

Campylobacter jejuni

Occupational and environmental exposure

Herbicides

Organic solvents
Hair dyes
Ultraviolet light

The difficulties of establishing a reproducible and clinically useful histological classification of NHL are reflected in the large number of classification systems to date. The current WHO classification stratifies according to cell lineage. Clinically, the most important factor is grade, which is a reflection of proliferation rate. High-grade NHL has high proliferation rates, rapidly produces symptoms, is fatal if untreated, but is potentially curable. Low-grade NHL has low proliferation rates, may be asymptomatic for many months before presentation, runs an indolent course, but is not curable by conventional therapy. Of all cases of NHL, 85% are either high-grade diffuse large-cell NHL or low-grade follicular NHL. Other forms of NHL, including mantle cell lymphoma and malt lymphomas, are less common.

WORLD HEALTH ORGANIZATION CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS

Precursor B-cell lymphoma

Precursor B-lymphoblastic lymphoma/leukemia

Mature B-cell lymphomas Chronic lymphocytic leukemia/small lymphocytic lymphoma
Lymphoplasmacytic lymphoma
Splenic marginal zone lymphoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
Nodal marginal zone B-cell lymphoma
Follicular lymphoma

Mantle cell lymphoma

Diffuse large B-cell lymphoma

Mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

Primary effusion lymphoma

Burkitt's lymphoma/leukemia

T/NK-CELL LYMPHOMAS

Precursor T-cell lymphoma

Precursor T-cell lymphoblastic leukemia/lymphoma

Blastic NK cell lymphoma

Mature T/NK cell lymphoma

Adult T-cell leukemia/lymphoma

Extranodal NK/T cell lymphoma, nasal type

Enteropathy-type T-cell lymphoma

Hepatosplenic T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides

Sézary syndrome

Primary cutaneous anaplastic large cell lymphoma

Peripheral T-cell lymphoma, unspecified

Angioimmunoblastic T-cell lymphoma Anaplastic large cell lymphoma

Clinical features Compared to Hodgkin lymphoma, NHL is often widely disseminated at presentation. Patients present with lymph node enlargement which may be associated with systemic upset: weight loss, sweats, fever and itching. Hepatosplenomegaly may be present. Extranodal disease is more common in NHL, with involvement of the bone marrow, gut, thyroid, lung, skin, testis, brain and, more rarely, bone. Extranodal disease is more common in T-cell disease, whilst bone marrow involvement is more common in low-grade (50-60%) than high-grade (10%) disease. The same staging system is used for both HL and NHL but NHL is more likely to be stage III or IV at presentation. Compression syndromes may occur; gut obstruction, ascites, superior vena caval obstruction and spinal cord compression may all be presenting features.

Non-Hodgkin's lymphomas can also manifest with a variety of immunologic abnormalities. For example, autoimmune hemolytic anemia and immune thrombocytopenia can be the presenting manifestations of non-Hodgkin's lymphoma, especially small lymphocytic lymphoma/chronic lymphocytic leukemia but also other subtypes, including diffuse large B-cell lymphoma. Peripheral neuropathies, often associated with overproduction of a monoclonal protein, can be seen in a variety of subtypes but are most characteristic of lymphoplasmacytic lymphoma and are also sometimes seen with POEMS syndrome (*poly*neuropathy, *organomegaly*, *endocrinopathy*, *M* protein, skin changes) associated with Castleman's disease. Paraneoplastic neurologic complications of non-Hodgkin's lymphoma include demyelinating polyneuropathy, Guillain-Barré syndrome, autonomic dysfunction, and peripheral neuropathy. Paraneoplastic syndromes associated with non-Hodgkin's lymphoma can affect the skin (e.g., pemphigus), kidney (e.g., glomerulonephritis), and miscellaneous organ systems (e.g., vasculitis, dermatomyositis, and cholestatic jaundice).

Investigations These are as for HL but in addition the following should be performed:

- Routine bone marrow aspiration and trephine.
- Immunophenotyping of surface antigens to distinguish T- and B-cell tumours. This may be done on blood, marrow or nodal material.
- Immunoglobulin determination. Some lymphomas are associated with IgG or IgM paraproteins which serve as markers for treatment response.
- Measurement of uric acid levels. Some very aggressive high-grade NHLs are associated with very high urate levels, which can precipitate renal failure when treatment is started.
- HIV testing. This may be appropriate if risk factors are present.

Differential diagnosis

The differential diagnosis in patients who are found to have non-Hodgkin's lymphoma is broad. Any cause of lymphadenopathy or splenomegaly can potentially be confused with non-Hodgkin's lymphoma. However, this confusion is resolved by appropriate biopsy. It is extremely important to recognize that the diagnosis of non-Hodgkin's lymphoma must be considered in patients with compatible clinical presentations and then confirmed by means of an adequate biopsy that is read by an experienced hematopathologist. The diagnosis should never be inferred, and patients should not be treated until the diagnosis is confirmed by biopsy.

Management **Low-grade NHL**

Asymptomatic patients may not require therapy. Indications for treatment include marked systemic symptoms, lymphadenopathy causing discomfort or disfigurement, bone marrow failure or compression syndromes. The options are:

- *Radiotherapy.* This can be used for localised stage I disease, which is rare.
- *Chemotherapy.* This is the mainstay of therapy. Most patients will respond to oral therapy with chlorambucil, which is well tolerated. More intensive intravenous chemotherapy in younger patients produces better quality of life but no survival benefit. Neither therapy will cure patients.
- *Monoclonal antibody therapy.* Humanised monoclonal antibodies can be used to target surface antigens on tumour cells, and induce tumour cell apoptosis directly. The anti-CD20 antibody rituximab has been shown to induce durable clinical responses in up to 60% of patients. At present in England and Wales it is only recommended as last-line therapy for stage III and IV follicular lymphoma. Synergistic effects are seen when treatment is combined with standard chemotherapy, and trials are under way to define its optimal usage.

Transplantation. Studies of autologous stem cell transplantation are in progress. Such high-dose therapy improves disease-free survival but longer follow-up is awaited before conclusions can be made about cure.

High-grade NHL

Patients with high-grade NHL need treatment at initial presentation:

Chemotherapy. The majority (> 90%) will need intravenous combination chemotherapy. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone) remains the mainstay of therapy. *Radiotherapy.* A few stage I patients without bulky disease may be suitable for radiotherapy. Radiotherapy is indicated for a residual localised site of bulk disease after chemotherapy, and for spinal cord and other compression syndromes.

- *Monoclonal antibody therapy.* When combined with CHOP chemotherapy, rituximab (R) increases the complete response rates and improves overall survival. The combination of R-CHOP is currently recommended for those with stage II or greater diffuse large-cell lymphoma as first-line therapy.

Transplantation. Autologous stem cell transplantation benefits patients with relapsed chemosensitive disease. The addition of autologous bone marrow transplantation to conventional salvage chemotherapy improves survival from 32% to 54% in relapsed high-grade NHL.

Prognosis Low-grade NHL runs an indolent remitting and relapsing course, with an overall median survival of 10 years. Transformation to a higher-grade NHL is associated with poor survival. In high-grade NHL, some 80% of patients overall respond initially to therapy but only 35% will have disease-free survival at 5 years. The prognosis for patients with NHL is further refined according to the international prognostic index (IPI). For high-grade NHL, 5-year survival ranges from 75% in those with low-risk scores (age < 60, stage I or II, one or fewer extranodal sites, normal LDH and good performance status) to 25% in those with high-risk scores (increasing age, advanced stage, concomitant disease and a raised LDH). Relapse is associated with a poor response to further chemotherapy (< 10% 5-year survival), but in patients under 65 years, stem cell transplantation improves survival.

MULTIPLE MYELOMA

This is a malignant proliferation of plasma cells. Normal plasma cells are derived from B cells and produce immunoglobulins which contain heavy and light chains. Normal immunoglobulins are polyclonal, which means that a variety of heavy chains are produced and each may be of kappa or lambda light chain type. In myeloma plasma cells produce immunoglobulin of a single heavy and light chain, a monoclonal protein commonly referred to as a paraprotein. In some cases only light chain is produced and this appears in the urine as Bence Jones proteinuria.

Although a small number of malignant plasma cells are present in the circulation, the majority are present in the bone marrow. The malignant plasma cells produce cytokines, which stimulate osteoclasts and result in net bone absorption. The resulting lytic lesions cause bone pain, fractures and hypercalcaemia. Marrow involvement can result in anaemia or pancytopenia. The aetiology of this condition is unknown.

CLASSIFICATION OF PLASMA CELL PROLIFERATIVE DISORDERS

- I. Monoclonal gammopathies of undetermined significance (MGUS)**
 - A. Benign (IgG, IgA, IgD, IgM, and rarely, free light chains)
 - B. Associated neoplasms or other diseases not known to produce monoclonal proteins
 - C. Biclonal gammopathies
 - D. Idiopathic Bence Jones proteinuria
- II. Malignant monoclonal gammopathies**
 - A. Multiple myeloma (IgG, IgA, IgD, IgE, and free light chains)
 1. Overt multiple myeloma
 2. Smoldering multiple myeloma
 3. Plasma cell leukemia
 4. Nonsecretory myeloma
 5. IgD myeloma

6. Osteosclerotic myeloma (POEMS syndrome)
7. Solitary plasmacytoma of bone
8. Extramedullary plasmacytoma
- B. Waldenström's macroglobulinemia
 1. Other lymphoproliferative diseases
- III.** Heavy chain diseases (HCDs)
 - A. γ -HCD
 - B. α -HCD
 - C. μ -HCD
- IV.** Cryoglobulinemia
- V.** Primary amyloidosis

Clinical features

Bone pain, particularly in the back or chest and less often in the extremities, is present at the time of diagnosis in more than two thirds of patients. The pain is usually induced by movement and does not occur at night except with change of position. The patient's height may be reduced by several inches because of vertebral collapse. Weakness and fatigue are common and are often associated with anemia. Fever is rare and, when present, is generally from an infection; in some patients the infection itself is the initial feature. Other symptoms may result from renal insufficiency, hypercalcemia, nephrotic syndrome, a radiculopathy, or amyloidosis.

Investigations The diagnosis of myeloma requires two of the following criteria:

- increased malignant plasma cells in the bone marrow
- serum and/or urinary paraprotein skeletal lesions. Bone marrow aspiration, plasma and urinary electrophoresis, and a skeletal survey are thus required.

RATIONALE FOR INVESTIGATIONS IN MULTIPLE MYELOMA

Problem	Investigations
Presence of lytic lesions, bone fractures	X-rays (skeletal survey)
Spinal cord compression	MRI spine
Presence of urine or plasma paraprotein	Blood and urine protein electrophoresis
Type of paraprotein	Blood and urine immunoelectrophoresis
Amount of paraprotein	Quantification of paraprotein
Degree of immune paresis	Plasma immunoglobulins
Presence of plasma cells in bone marrow	Bone marrow aspiration and trephine
Degree of bone marrow failure	Full blood count
Renal function	Urea and electrolytes, creatinine, urate
Presence of hypercalcaemia	Blood calcium Albumin
Degree of haemostasis	Bleeding time Coagulation screen

POINTS TO NOTE IN THE DIAGNOSIS OF MYELOMA:

- Plasma alkaline phosphatase and the bone scan are normal in the absence of fractures or bone repair
- Serum β_2 -microglobulin estimations may provide a useful assessment of prognosis
- Normal immunoglobulin levels, i.e. absence of immune paresis, should cast doubt on the diagnosis
- Only about 5% of patients with an ESR persistently above 100 mm/hr have myeloma

Management If patients are asymptomatic, treatment may not be required. Otherwise, treatment consists of the measures described below.

Immediate support High fluid intake to treat renal impairment and hypercalcaemia.

- Analgesia for bone pain.
- Bisphosphonates for hypercalcaemia and to delay other skeletal related events.
- Allopurinol to prevent urate nephropathy.
- Plasmapheresis, as necessary, for hyperviscosity.

Chemotherapy In frail older patients, melphalan is an effective oral therapy, whilst in younger patients treatment with intravenous agents may improve response. Higher doses of intravenous melphalan appear to be well tolerated even in patients over 65 years and may produce better clinical responses.

Treatment is administered until paraprotein levels have stopped falling. This is termed 'plateau phase' and may last for weeks or years. Successive relapses respond less well to treatment.

Radiotherapy This is effective for localised bone pain not responding to simple analgesia and for pathological fractures. It is also useful for the emergency treatment of spinal cord compression complicating extradural plasmacytomas.

Transplantation 'The addition of autologous bone marrow transplantation to conventional intravenous chemotherapy improves survival from 42 to 54 months.'

Standard treatment does not cure myeloma. Autologous stem cell transplants improve quality of life and prolong survival. All suitable patients under 65 years should be offered intravenous chemotherapy to maximum response and then an autologous stem cell transplant. Allogeneic bone marrow transplantation may cure some patients and should be considered in those under the age of 55 years with a sibling donor. Reduced-intensity allografting may improve outcomes by reducing transplant-related mortality and extending the upper age limit.

Bisphosphonates Long-term bisphosphonate therapy reduces bone pain and skeletal events. These drugs protect bone and may cause apoptosis of malignant plasma cells. **Thalidomide.** This drug has anti-angiogenic effects against tumour blood vessels and also immunomodulatory effects. At low doses it has been shown to be effective against refractory myeloma and when combined with dexamethasone, response rates over 50% are described. Trials are currently under

way to investigate the use of thalidomide as an adjunct to other treatments earlier in the natural history of the disease. It can cause somnolence, constipation and a peripheral neuropathy. It is vital that females of child-bearing age use adequate contraception as it is teratogenic. Other new agents include the proteasome inhibitor bortezomib which has also shown activity in advanced myeloma, and thalidomide derivatives which are currently being evaluated in clinical trials.

Prognosis

The median survival of patients receiving standard treatment is approximately 40 months. Poor prognostic features include a high β_2 -microglobulin, low albumin, a low haemoglobin or a high calcium at presentation. Autotransplantation improves survival and quality of life by slowing the rate of progression of bone disease. Less than 5% of patients survive longer than 10 years with standard treatment.

1. Which cells are called plasmacytomas?

- A. T-killers.
- B. neutrophils.
- B. B cells after antigen stimulation.
- G. mast cells.
- D. erythroblasts.

2. What is a complement?

- A blood coagulation factor.
- B. inactive protease complex.
- B. receptor leukocytes.
- G. vasoactive substances.
- D. antigen.

3. That is synthesized in plasma cells in response to antigenic stimulation?

- A antibodies.
- B. hormones.
- B. cholesterol.
- G. cytokines.
- D. blood clotting factors.

4. What is the main immunoglobulin class?

- A. IgM.
- B. IgG.
- B. IgA.
- G. IgE.
- D. IgD.

5. Humoral immune responses, with the participation of complement leads to:

- A bacterial cell phagocytosis.
- B. agglutination of bacterial cells.
- B. lysis of bacterial cells.
- G. did not affect the bacteria.
- D. mutations of bacteria.

6. Which of cells did not belong to the responder?

- A. B cells.
- B. T-lymphocytes.
- B. macrophages.
- G. neutrophils.
- D. erythrocytes.

7. What body does not belong to the lymphatic system?

- A lymphatic vessel.
- B. spleen.
- B. lymph node.
- G. marrow.
- D. Peyer's patches.

8. Which belong to the protein fraction of blood antibodies?

- A. β -globulins.
- B. γ -globulins.
- B. α_1 -globulins.
- G. α_2 -globulins.
- D. albumins.

9. With the mediation of what cells are stimulated B-lymphocyte antigens?

- A pluripotent stem cells.
- B. T-killers.
- B. T-suppressor lymphocytes.
- H. T-helper lymphocytes.
- D. basophilic granulocytes.

10. Where the maturation of B cells?

- A liver
- B. lymph nodes.
- B. spleen.
- G. red marrow.
- D. yellow marrow.

1. What differs from lymphoma leukemia?
 - A. in leukemia is no lymph node involvement.
 - BS in lymphomas no signs of general intoxication.
 - B. does not apply in lymphoma treatment with cytostatics.
 - G. in lymphomas primary pathological process develops outside the boundaries of the bone marrow.
 - D. lymphoma not complicated infectious and inflammatory diseases.

2. Which cells are characteristic granulomas in Hodgkin lymphoma?
 - A. Botkin cell-basket cells.
 - B. Reed-Sternberg cells.
 - B. platelets.
 - G. erythrocytes.
 - DA blasts.

3. What is most characteristic symptom of the initial period of Hodgkin's disease?
 - A. splenomegaly.
 - B. fever.
 - B. pain in the lumbar region.
 - G. night sweats.
 - D. lymph nodes.

4. What features have enlarged lymph nodes with chlamydia?
 - A dense, painless, fixed, welded to the skin.
 - B. soft, painful, moving, not welded to the skin.
 - B. plotnoelastichnye, painless, mobile, not welded to the skin.
 - G. tight, painful, flushed skin over the lymph nodes.
 - D. soft, painful, still.

5. To what stage of Hodgkin's disease is characterized by diffuse damage internal organs?
 - A. I stage.
 - B. Stage II.
 - B. III stage.
 - G. IV stage.
 - D. internal organ with chlamydia do not happen.

6. Which method of research is required to confirm the diagnosis of non-Hodgkin lymphoma?
 - A. ultrasound.
 - B. sternal puncture.
 - B. lymph node biopsy.
 - G. liver biopsy.

D. CBC.

7. Which cells are substrates for non-Hodgkin lymphoma tumor?

- A. lymphocytes.
- B. neutrophils.
- B. monocytes.
- G. erythrocytes.
- D. platelets.

8. In what disease can be transformed lymphoma?

- A lymphosarcoma.
- B. acute lymphoblastic leukemia.
- B. Chronic lymphocytic leukemia.
- G. lymphadenitis.
- D. myeloma.

9. For what disease is characterized hyperproteinemia?

- A lymphosarcoma.
- B. Hodgkin's disease.
- B. Chronic lymphocytic leukemia.
- G. Non-Hodgkin's lymphoma.
- D. myeloma.

10. For what disease is characterized detection in urine Bence-Jones?

- A multiple myeloma ..
- B. Hodgkin's disease.
- B. chronic glomerulonephritis.
- G. acute leukemia.
- D. autoimmune hemolytic anemia.

Situational problems.

№ 1

The patient, aged 48, complains of weakness, sweating, intense itching of the skin, fever. OBJECTIVE: pale skin and mucous membranes, cervical lymph nodes - lively, densely-elastic, about the size of the Greek walnut, painless, not welded to the skin, the body temperature $38,3^{\circ}\text{C}$. Common blood: red blood cells - $3,0 \times 10^{12} / \text{L}$, hemoglobin - $100 \text{ g} / \text{L}$, white blood cells - $14 \times 10^9 / \text{L}$, eosinophils - 6%, basophils - 3%, stab - 11%, segmented - 69%, lymphocytes - 7%, monocytes - 4%, platelets - $280 \times 10^9 / \text{L}$, ESR - $37 \text{ mm} / \text{h}$ What method of the survey should be used to verify the diagnosis?

- A. Sternal puncture
- B. Muscle biopsy
- B. lymph node biopsy
- G. Chest X-ray
- D. Spinal Tap

N 2.

The sick 57-year-old suffered for lymphoma, clinical stage IIIES. Which treatment is appropriate to apply in this case?

- A. radiation therapy.
- B. polychemotherapy.
- B. splenectomy.
- D. combination of radiation therapy and chemotherapy.
- D. steroids.

№ 3

The patient, aged 28, complains of weakness, bone pain, frequent respiratory infections, and dizziness. OBJECTIVE: pale skin and mucous membranes, ossalgia. Common blood: red blood cells - $2,7 \times 10^{12} / \text{L}$, hemoglobin - $80 \text{ g} / \text{L}$, CPU - 0.9, reticulocytes - 0.5%, leukocytes - $5 \times 10^9 / \text{L}$, eosinophils - 1%, basophils - 3 %, stab - 7%, segmented - 60%, lymphocytes - 23%, monocytes - 2% plasma cells - 4%, thrombocytes - $280 \times 10^9 / \text{L}$, ESR - $64 \text{ mm} / \text{h}$ The total blood protein - $120 \text{ g} / \text{L}$. Urinalysis: protein 2.5 g per day. Radiography of the skull: foci of destruction of bone. The diagnosis?

- A. Multiple myeloma
- B. Chronic lymphocytic leukemia
- B. Acute Lymphocytic Leukemia
- G. Acute Myelogenous Leukemia
- D. Waldenstrom's disease

№ 4

The patient, aged 38, complains of weakness, sweating, intense itching of the skin, fever. OBJECTIVE: pale skin and mucous membranes, cervical lymph nodes - mobile, close-elastic, about the size of the Greek walnut, painless, not welded to the skin, the body temperature $38,3^{\circ}\text{C}$. Common blood: red blood cells - $3,0 \times$

1012 / L, hemoglobin - 100 g / L, white blood cells - 14×10^9 / L, eosinophils - 6%, basophils - 3%, stab - 11%, segmented - 69%, lymphocytes - 7%, monocytes - 4%, platelets - 280×10^9 / l, ESR - 37 mm / h What morphological data are likely to be obtained in the lymph node biopsy?

- A. Plasma cells
- B. Taurus Heinz
- B. Cells Botkin-basket cells
- Mr. Taurus Melora
- J. Berezovsky-Sternberg cells

№ 5

The patient, aged 28, complains of weakness, bone pain, frequent respiratory infections, and dizziness. OBJECTIVE: pale skin and mucous membranes, ossalgia. Common blood: red blood cells - $2,7 \times 10^{12}$ / L, hemoglobin - 80 g / l, CPU - 0.9, reticulocytes - 0.5%, leukocytes - 5×10^9 / L, eosinophils - 1%, basophils - 3 %, stab - 7%, segmented - 60%, lymphocytes - 23%, monocytes - 2% plasma cells - 4%, platelets - 280×10^9 / l, ESR - 64 mm / h The total blood protein - 120 g / l. Urinalysis: protein 2.5 g per day. Radiography of the skull: foci of destruction of bone. What method of investigation to confirm the diagnosis would be most informative?

- A serum protein electrophoresis
- B. sternal puncture
- B. lymph node biopsy
- G. Reaction Waal - Rose
- D. Schilling test

№ 6

Patient K., 24 years, 2 months ago ago noticed enlarged lymph node in the neck to the left, then there was weakness, sweating, itching, fever up to 39°C. Application sulfadimezin and oksatsilina no effect. On examination, the skin of normal color, left on the side of the neck lymph node two and a diameter of 1.5 cm 2, medium density, painless. The internal organs changes were not identified. Blood: red blood cells - $4,2 \times 10^{12}$ / L, hemoglobin - 132 g / l, CPU - 0.9, WBC - $9,6 \times 10^9$ / L, eosinophils - 5%, stab - 8%, segmented - 73% , lymphocytes - 10%, monocytes - 4%, ESR - 32 mm / h Previous diagnosis?

- A. Chronic lymphocytic leukemia
- B. Infectious mononucleosis
- B. Non-Hodgkin's Lymphoma
- G. Multiple myeloma
- D. Hodgkin

№ 7

The patient 43 years diagnosed non-Hodgkin's lymphoma. What changes in the clinical analysis of blood are characteristic of this disease?

- A hypochromic anemia.
- B. neutrophilic leukocytosis.
- B. leukopenia.
- G. lymphocytosis.
- Lymphopenia D. ..

№ 8

The patient, 24 years, 3 months ago ago limfovuzol noticed an increase in the neck to the left. In reviewing the normal color of skin, left on the side of the neck two limfovuzla 2 cm in diameter, medium density, painless. The internal organs changes were not identified. Blood: red blood cells - $4,2 \times 10^{12} / L$, hemoglobin - 132 g / l, CPU - 0.9, WBC - $9,6 \times 10^9 / L$, eosinophils - 5%, stab - 8%, segmented - 73% , lymphocytes - 10%, monocytes - 4%, ESR - 32 mm / h Diagnosed with Hodgkin's disease, clinical stage I. What is the optimal treatment strategy?

- A. polychemotherapy and radiotherapy
- B. Radiation therapy
- B. blood transfusion
- G. Plasmapheresis
- D. Hormone, cytostatics

№ 9

The patient, aged 47, suffers from non-Hodgkin's lymphoma. The general condition of the patient is satisfactory. What medication are useful for monotherapy?

- A. Vincristine.
- B. Fludarabine.
- B. Imatinib.
- G. Prednisolone.
- D. Mustargen.

№ 10

A patient aged 34, complained of an increase in the area limfovuzlov neck, feeling of heaviness in the abdomen, general weakness. OBJECTIVE: asymmetrical lymph nodes in the neck - a conglomerate ossalgiya, hepatosplenomegaly. Hemogram: anemia, accelerated ESR, leukocytosis, neutrophilia, eosinophilia, lymphopenia, monocytosis. Lymph node puncture: identifying Reed-Sternberg cells. Your diagnosis?

- A. Chronic lymphocytic leukemia
- B. Acute lymphoblastic leukemia
- B. reactive lymphadenopathy
- G. Hodgkin
- D. Non-Hodgkin's Lymphoma

№ 11

Patient P., 62 years old, accidentally groped in her left subclavian fossa compact, measuring a little more than a pea, mobile, not soldered to the skin nodule. On questioning revealed that in the last 6 months lost 12 kg. Marked weakness, reduced ability to work, loss of appetite. What research is a priority for the diagnosis?

- A. Esophagogastroduodenoscopy
- B. Aspiration lymph node
- B. sternal puncture
- G. Chest X-ray
- D. Ultrasound of the abdomen

№ 12

The patient, aged 54, suffers from multiple myeloma. What medications are appropriate to assign to chemotherapy in the first place?

- A. Chlorambucil and tsiklofosomid
- B. Rituximab and fludarabine
- W. α 2-interferon and dexamethasone
- G. Melphalan and prednisone
- D. Allopurinol and calcitonin

№ 13

Patient N., 27, turned to the clinic complaining of increasing limfovuzlov neck to the right and in the inguinal area, night sweats, fever above 38 ° C. Morphologic study of biopsy lymph node cells were identified Berezovsky-Stenberg. What is the diagnosis in this patient?

- A. Chronic lymphocytic leukemia
- B. Hodgkin
- B. Malignant Lymphoma
- G. Tuberculosis of lymph nodes
- J. Cancer metastasis to the lymph nodes

№ 14

The man, 49 years old, with preventive screening examination in the blood revealed increased erythrocyte sedimentation rate, and in the analysis of urine - proteinuria. An objective examination of any signs of disease were found. Further examination: blood chemistry - increasing the level of total protein in urine - Bence-Jones protein. The diagnosis?

- A. Multiple myeloma
- B. Hodgkin
- B. Acute leukemia.
- G. Chronic glomerulonephritis.
- D. Primary amyloidosis

№ 15

In patients with multiple myeloma, which takes melphalan and prednisone, after hypothermia cough, shortness of breath, fever. After the clinical laboratory and radiological examinations diagnostovana pneumonia. What treatment strategy should be followed in this case?

- A. Change regimen
- B. Go to monotherapy with glucocorticoids
- B. antibiotics and drugs detoxification
- D. Conduct a course of radiotherapy
- D. In addition to appoint $\alpha 2$ -interferon

QUESTIONS

Task 1

A 70-year-old male complains of 2 months of low back pain and fatigue. He has developed fever with purulent sputum production. On physical exam, he has pain over several vertebrae and rales at the left base.

Laboratory results are as follows:

Hemoglobin: 70 g/L

MCV: 86 fL (normal 86 to 98)

WBC: $12 \times 10^9/L$

BUN: 44 mg/dL

Creatinine: 3.2 mg/dL

Ca: 11.5 mg/dL

Chest x-ray: LLL infiltrate

Reticulocyte count: 1%

The most likely diagnosis is

- a. Multiple myeloma**
- b. Lymphoma
- c. Metastatic bronchogenic carcinoma
- d. Primary hyperparathyroidism

Task 2

The definitive diagnosis is best made by

- a. 24-h urine protein
- b. Greater than 10% plasma cells in bone marrow**
- c. Renal biopsy
- d. Rouleaux formation on blood smear

Task 3

Renal insufficiency may have developed in this patient secondary to

- a. Obstruction of collecting tubules by Bence-Jones protein
- b. Hypercalcemia

- c. Amyloid deposition
- d. Plasma cell infiltration of the kidney
- e. All of the above**

Task 4

A 68-year-old man seeks evaluation for fatigue, weight loss, and early satiety that have been present for about 4 months. On physical examination, his spleen is noted to be markedly enlarged. It is firm to touch and crosses the midline. The lower edge of the spleen reaches to the pelvis. His hemoglobin is 111 g/L, and hematocrit is 33.7%. The leukocyte count is $6.2 \times 10^9/\text{L}$, and platelet count is $220 \times 10^9/\text{L}$. The white cell count differential is 75% PMNs, 8% myelocytes, 4% metamyelocytes, 8% lymphocytes, 3% monocytes, and 2% eosinophils. The peripheral blood smear shows teardrop cells, nucleated red blood cells, and immature granulocytes. Rheumatoid factor is positive. A bone marrow biopsy is attempted, but no cells are able to be aspirated. No evidence of leukemia or lymphoma is found. What is the most likely cause of the splenomegaly?

- A. Chronic idiopathic myelofibrosis**
- B. Chronic myelogenous leukemia
- C. Rheumatoid arthritis
- D. Systemic lupus erythematosus
- E. Tuberculosis

Task 5

Which of the following carries the best disease prognosis with appropriate treatment?

- A. Burkitt's lymphoma
- B. Diffuse large B cell lymphoma
- C. Follicular lymphoma
- D. Mantle cell lymphoma
- E. Nodular sclerosing Hodgkin's disease**

Task 6.

In an office visit for an annual checkup, a 46-year-old man reports that he has had malaise and intermittent sweats for the past few months but has been able to continue his job as a high school teacher. Two years ago he was treated for stage III diffuse large-cell non-Hodgkin's lymphoma with six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and attained complete remission. He takes simvastatin for hypercholesterolemia and hydrochlorothiazide for hypertension. On physical examination, he has lymphadenopathy: a 3-cm right axillary node and a 2-cm right supraclavicular node. His spleen tip is palpable. Laboratory evaluation shows mild normochromic, normocytic anemia and an elevated serum lactate dehydrogenase level. CT scans of his chest and abdomen reveal additional mediastinal and retroperitoneal lymphadenopathy. What is the best next step in this patient's management?

- A. A 2-week course of oral antibiotics
- B. Referral for salvage chemotherapy and autologous stem cell transplantation**
- C. A repeat physical examination and CT scans in 3 months
- D. Referral for treatment with investigational agents
- E. A repeat course of CHOP

Task 7.

A 74-year-old woman is anemic with hemoglobin of 10.5 g/dL. She has symptoms of tingling in her feet and back discomfort. X-rays of her spine reveal osteopenia and multiple lytic lesions. She has an immunoglobulin G (IgG) spike on serum protein electrophoresis.

- A. Thalassemia
- B. Lymphoma
- C. Thiamine deficiency
- D. Acute hemorrhage
- E. Myeloma**

Task 8.

A 60-year-old man notices right-sided chest pain after sneezing. The pain is made worse with breathing, but he reports no fever, sputum, or cough. Recently, he has been experiencing back discomfort and easy fatigue on exertion. On examination, the heart sounds are normal and lungs are clear. The left 6th rib is tender on palpation. Which of the following is the most likely diagnosis?

- A. Aneurysmal bone cyst
- B. Multiple myeloma**
- C. Lymphosarcoma
- D. Prostatic metastases
- E. Hyperparathyroidism

Further reading:

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5. Davidson's principles of medicine, 20th edition / Edited by Nicholas A. Boon, Nicki R. Colledge, Brian R. Walker. Elsevier Limited – 2006. – 2456 p.
6. Cecil Medicine, 23rd edition / Edited by Lee Goldman, Dennis Ausiello. Saunders Elsevier. – 2007. – 2178 p.
7. Kumar & Clark: Clinical Medicine, 6th edition / Edited by Parveen Kumar, Michael Clark. Elsevier, Inc. – 2006. – 1862 p.