**Hemoblastosis**

**Hemoblastosis** represents a group of tumors which develop from hematopoietic cells. Main pathogenetic mechanism is represented by disorders of leucocyte maturation due to a block of differentiation. Disorders of leucocyte maturation with increased leucocytopoiesis develops under the influence of some cancerogenic factors which can lead to severe multiplication and differentiation disorders of hematopoietic cells with uncontrolled multiplication of atypical cells which in addition have low ability to maturate. Release of these leucocytes from bone marrow into peripheral blood is the result of disturbed osseo-medullary permeability.

Hemoblastosis in which bone marrow is invaded by tumoral cells originating from hematopoietic tissue and which lead to diffuse injury of bone marrow are called *leucosis****.***

**Leucosis**

*Leucosis* represents malignant neoplasm of cell derived from hematopoietic progenitors, having as general manifestations abundant proliferation of hematopoietic tissue (*hyperplasia*), lost capacity of differentiation and maturation of hematopoietic cells (*anaplasia*) and invasion of non-hematopoietic tissue with tumoral cells (*metaplasia*).

They are characterised by diffuse replacement of bone marrow with immature, neoplastic, unregulated cells, which in most cases spill out into the peripheral blood there these are seen in large number. Because leukemic cells are immature and poorly differentiated, they proliferate rapidly and have a long lifespan, they do not function normally and interfere with maturation of normal blood cells, circulate in the bloodstream, cross the blood-brain barrier and infiltrate many tissues and organs. Usually, leukemic cells infiltrate the liver, spleen, lymph nodes and other tissues throughout the body, leading to increased sizes of these organs.

**Etiology**of leucosis is multilaterally studied but not yet definitively clarified.

Nowadays there are more theories regarding etiology of leucosis:

1. *Iatrogenic factors*. Ironically, radiation therapy and certain forms of chemotherapy used to treat cancer increase the risk of subsequent myeloid and lymphoid neoplasms. This association stems from the mutagenic effects of ionizing radiation and chemotherapeutic drugs on hematolymphoid progenitor cells. In experimental condition in laboratory animals leucosis can be reproduced using radiation.
2. *Chemical factors* – in laboratory animals there is possible to induce leucosis by administration of some chemical cancerogenic substances. It was established that leucosis is more frequent in people who activated during life in chemical industry having direct contact with benzole and other organic solvents.
3. *Role of viruses*. Three lymphotropic viruses human T-cell leukemia virus-1 (HTLV-1), Epstein-Barr virus (EBV), and Kaposi sarcoma herpes virus/human herpes virus-8 (KSHV/HHV-8) have been implicated as causative agents in particular lymphomas. HTLV-1 is associated with adult T-cell leukemia/lymphoma. EBV is found in a subset of Burkitt lymphoma, 30% to 40% of Hodgkin lymphoma (HL), many B-cell lymphomas arising in the setting of T-cell immunodeficiency, and rare NK-cell lymphomas. In addition to Kaposi sarcoma, KSHV is uniquely associated with an unusual B-cell lymphoma that presents as a malignant effusion, often in the pleural cavity.
4. *Inherited genetic factors*. Individuals with genetic diseases that promote genomic instability, such as Bloom syndrome, Fanconi anemia, and ataxia telangiectasia, are at increased risk of acute leukemia. In addition, both Down syndrome (trisomy 21) and type I neurofibromatosis are associated with anincreased incidence of childhood leukemia.
5. *Chronic immune stimulation*. Several environmental agents that cause localized chronic immune stimulation predispose to lymphoid neoplasia, which almost always arises within the inflamed tissue. Examples include the associations between *H. pylori* infection and gastric B-cell lymphomas, and gluten-sensitive enteropathy and intestinal T-cell lymphomas. This can be contrasted with HIV infection, which is associated with an increased risk of B-cell lymphomas that may arise within virtually any organ. Early in the course, T-cell dysregulation by HIV infection causes a systemic hyperplasia of germinal center B cells that is associated with an increased incidence of germinal center B-cell lymphomas. In advanced infection (acquired immunodeficiency syndrome), severe T-cell immunodeficiency further elevates the risk for B-cell lymphomas, particularly those associated with EBV and KSHV/HHV-8.
6. *Smoking.* The incidence of acute myeloid leukemia is increased 1.3- to 2-fold in smokers, presumably because of exposure to carcinogens, such as benzene, in tobacco smoke.

So, in conclusion every specific form of leucosis can be determined by exogenous factors or by endogenous predisposition, but more frequent there is a combination of these factors.

**Leucosis pathogeny** involves following phenomena and pathological processes:

1. Tumoral atypia;
2. Clonal origin;
3. Tumoral progression.

**Tumoral atypia** – First particularity in leucosis pathogeny is transformation of genetic normal program of the cell in the program of tumoral atypia determined by changes at the level of genome under the influence of tumoral factors. In leucosis, normal hematopoietic cells are replaced with *leukemic cells*. These cells just apparently are like normal ones, really their chromosomal structure is modified this giving them malign properties. Essential forms of cell atypia are: growth, structural, biochemical and functional.

*Growth atypia* is characterised by the fact that in the bone marrow there is a process of pathological “rejuvenation” of hematopoietic cells, caused by a diffuse growth of blast cells – atypical leukemic cells besides normal hematopoietic cells. Blast atypical cell in leucosis just apparently mimic normal cells, really these are characterised by a high proliferative activity concomitantly with reduced or even stopped process of maturation. Examination of bone marrow, obtain by bone aspiration, shows that more than 20% of medullary cells are “blast” leukemic cells. In these, there can be found a dissociation between nucleus and cytoplasmatic organelles maturation. There can be attested presence of Auer corpuscle, pronounced basophilia of the cytoplasm, intense auzurophilic granulation (primary granules) meantime differentiation of secondary granules is disturbed.

Peripheral blood in leukemias is characterised by a complex of characteristic changes:

1. Invasion of the blood with blast cells as result of enhanced proliferation of atypical leukemic cells. There is increased release of these cells from the bone marrow as result of increased histo-hemic barrier permeability. Presence of leukemic cells in the peripheral tissue denotes certainly diagnosis of leucosis and when there is invasion of peripheral blood with blast cells there is certainly acute leucosis. In function of total number of leucocytes and blast cells in peripheral blood there can be distinguished following forms of leucosis:

* *Leukemic leucosis* – characterised by increased leucocyte count above 100000/mm3 in association with a very high number of blast leukemic cells in the peripheral blood;
* *Subleukemic leucosis* – characterised by increased leucocyte count till 80000/mm3 associated with high number of leukemic blast cells in peripheral blood;
* *Leucocytopenic leucosis* – characterised by decreased leucocyte count below 5000/mm3 associated with presence of leukemic blast cells in peripheral blood;
* *Aleukemic leucosis*– characterised by normal leucocyte count - 5000-6000/mm3, there are no leukemic blast cells in peripheral blood, but there is increased number of atypical leukemic blast cells in the bone marrow.

1. Presence of so-called *“Hiatus leukemicus*” – hematological symptom characteristic for acute myeloblastic leucosis, characterised by invasion of the peripheral blood with blast leukemic cells which circulate with mature cells, meantime intermediary young leucocytes (promyelocytes, myelocytes) are lacking. This phenomenon reflects disorders of leukemic cell proliferation and maturation blockage of these.
2. Presence of so-called “*eosino-basophilic association*” – hematologic symptom characteristic for chronic myeloid leucosis, characterised by concomitant increased count of eosinophils and basophils in peripheral blood, this denoting differentiation and maturation of leukemic atypical blast cells from the series of eosinophils and basophils.
3. Presence of so-called “*Botkin-Gumpreht amprents*” - specific spots (nuclear remnants of chromatin), which can be found on blood smear in patients with chronic lymphoid leucosis as result of increased lability of nuclear membrane in lymphoblast cells to mechanical factors.
4. Presence of azurophilic granulation and Auer corpuscles – numerous and big auzurophilic granulation in the cytoplasm of neutrophils with some inclusions having a stick shape resembling crystal. This is a characteristic hematologic symptom in acute myeloblast leucosis.

**Structural atypia** by one hand refers to changes at the level of cell – shape, size (nucleus size), relation between nucleus size and cytoplasm (*cellular atypia*), and changes of quantitative correlation by other hand, in other words correlation between number of leukemic cells and other hematopoietic cells which can exist in that form of leucosis (*tissular atypia*).

Ex. in acute myeloblastic leucosis there can be found 3 cell population of circulating neutrophils: neutrophils which have just ausurophilic granulation, without specific secondary granulation; neutrophils which have only secondary specific granulation without primary ausurophilic granulation; neutrophils with both, primary and secondary granulation, but these granulation lack specific peroxidase. All these confirm the fact that in acute myeloblastic leucosis there is disturbed normal process of neutrophil differentiation.

Structural atypia can be determined by changes at level of genome that will manifest by disorders of nuclear acid synthesis, protein, fat as well as other factor synthesis, which are needed for plastic processes in hematopoietic cells.

**Biochemical atypia**. Acute myeloblastic leucosis is characterised by disorders of some enzyme synthesis, for ex. acid phosphatase, myeloperoxidase these leading to metabolic disorders. In lympholeucosis, atypical B lymphocytes can synthesize abnormal immunoglobulins (lack of bi-sulphidic bond) – *paraproteinemia*.

In leucosis, there can be found *dysproteinemia* – changed correlation between albumins and globulins with overproduction (by leukemic cells) of immunoglobulins. All these changes can be explained by changed genetic information in leukemic atypical cells with mutations at the level of some genes responsible for synthesis of proteinic molecules qualitatively modified, this leading to diverse metabolic disturbances.

**Functional atypia** – in leucosis this represents dysfunction of leukemic cells which lose their functional specific activity, manifested by diminished phagocytic function, disorders of mechanisms necessary for realization of humoral and cellular immunity with development in such patients of immunodeficient states characterised by remarked reduction of anti-tumoral and anti-infectious resistance.

Dysfunction of leukemic cells is the result of maturation disorders of leucocytes, characterised both by diminished activity or structural changes of leucocyte enzymes (enzymopathies) or changes at the level of leucocyte membrane (mebranopathies). Moreover, totality of changes determined by tumoral atypia leads as well to development of many non-specific manifestations in leucosis. Ex. inflammation in patients with leucosis develops with prevalence of alterative reactions, exudative and even necrotic reactions. Such an inflammation evolution in leucosis can be explained by deep suppression of immune mechanisms, suppression of antibodies synthesis, increased vessel wall permeability and other changes developed as result of extramedullary foci of hematopoiesis.

**Clonal origin of leucosis** represents the second important particularity of leucosis development mechanism, which stipulates that leukemic cells represents some clones – in other words colonies of cells with origin from a single mutant cell which preserve all characteristics of this. Moreover, these have origin from “stem” cell, easily are released into peripheral blood and can form colonies everywhere in hematopoietic tissue. Colonies forming determined the process of metastasis even from the beginning of tumoral process, this phenomenon not being characteristics for cancer or sarcoma, when metastasis is characteristic just for late stages of development.

There are many facts that in leucosis there are no disturbances of hematopoietic tissue activity, no disturbances of normal hematopoietic cells maturation, but main pathogenetic mechanisms is related to a mutant cell that will later lead to development of many leukemic cells that will form the *leukemic clone*.

**Tumoral progression** represents the third particularity of leucosis pathogeny. On the basis of tumoral progression there is increased chromosomal variability of leukemic cells, this leading to development of new mutant clones in primary-maternal clone such determining increased variability of leukemic clones.

There is clear scientifically that, from the moment of primary injury of the cell till subsequent transformation of all siblings in tumoral cells there should be a series of changes at the level of genetic apparatus of the cells.

So, tumoral progression, in essence, represents a mechanism of growth, a mechanisms for intensification of malignancy of tumoral process. Hemoblastosis, usually passes 2 phases in their development: a) *monoclonal phase* – also called benign form (light form) and b) *polyclonal phase* – so-called malignant phase (severe phase)

There can be distinguished following laws of tumoral progression:

1. Transformation of monoclonal leucosis in polyclonal one;
2. Transformation of aleukemic leucosis in leukemic one;
3. Metastasis of extramedullary hemoblastosis in the bone marrow;
4. Metastasis of leukemic cells at distance from hematopoietic organs in extramedullary tissues;
5. Suppression of normal hematopoiesis with development of anemia, thrombocytopenia and leucocytopenia;
6. Replacement of differentiated cells with blast cells marks transformation of aleukemic leucosis in leukemic one;
7. Loss of biochemical specificity of blast cells this making them to become unidentified with cytochemical specific reactions;
8. Changed shape of nucleus in blast cells – from round to an irregular shape;
9. Extramedullary metastasis of hemoblastosis denotes development of a new clone of leukemic cells;
10. Increased resistance of leukemic cells to cytostatic treatment denotes transformation of monoclonal leucosis in polyclonal one; this is a new qualitative stage (more severe, more malign) in development of leucosis.

So, tumoral progression represents qualitative changes in development stages of leucosis as result of increased variability of genetic apparatus of leukemic cells this leading to progression to polyclonal form with development of new mutant clones. These represent specific mutations (characteristic for every type of leucosis) responsible for cell proliferation by one hand, and stages of hematopoietic tissue differentiation by other hand. Tumoral instability of genotype characterised by new tumoral mutations, lead to repeated mutations with selection of new tumoral clones which have new properties. So, first, there is monoclonal proliferation, this representing benign leucosis, later in leukemic cells there will be new mutations with development of a subclone of tumoral leukemic cells marking polyclonal proliferation and the stage of malignant leucosis.

**Classification of leucosis** There can be recognized: a) leucosis and b) hematosarcomas.

*Leucosis* represent tumors which have origin in hematopoietic cells of bone marrow, and *hematosarcomas* – have origin from extramedullary hematopoietic cells. Besides these, hematosarcomas are characterised by a local growth of tumoral cells without spread of tumoral cells through hematopoietic tissue till development of metastasis.

On the basis of modern leucosis classification there are more criteria:

* In function of cell morphology which represent tumoral mass;
* Degree of cell differentiation disturbances, both structurally (structure of nuclei, nucleo-cytoplasmatic correlation) and cytochemical (specific cytochemical reactions) on the basis of which there can be recognized *leucosis of myeloid lineage* and *lymphoid lineage*. *Biphenotypic leucosis* demonstrate characteristics of both lymphoid and myeloid lineages.
* Number of blastic cells in the bone marrow and in the peripheral blood, immunological phenotype and genetic particularities of these leukemic cells;
* Evolution and degree of tumoral progression of leucosis.

Anyway, leucosis commonly are classified according to their predominant cell type (lymphocytic or myelocytic) and whether the condition is acute or chronic. *Lymphocytic leukemia* involves immature lymphocytes and their progenitors that originate in the bone marrow but infiltrate lymph nodes and spleen, CNS and other peripheral tissue. *Myelocytic leukemia* involves the pluripotent stem cell in the bone marrow, interfere with maturation of blood cells and involve all granulocyte, erythrocyte and thrombocytes lineages.

Should be mentioned that, on the basis of classification of leucosis in acute and chronic forms, there is degree of differentiation of cells at the level of bone marrow as well as morphologic qualitative changes of cells released in peripheral blood, but no evolution of leucosis.

**General clinical manifestations of leukemias**

(characteristic for all myelocytic and lymphocytic leukemias)

* *Fever* which is frequent in leukemic patients can be explained by release of secondary pyrogen – interleukin -1 – as result of intensified lysis of atypical leucocyte and/or persistence of respiratory or urinary infections, mouth ulceration.
* *Hemorrhagic syndrome* (petechiae, ecchymosis, gingival bleeding, epistaxis) in leucosis is determined by thrombocytopenia, sometimes can be the result of intramural metastasis leading to increased vessel fragility and propensity to bleeding.
* *Hematologic abnormalities* mainly *anemia* and *thrombocytopenia-* both have similar mechanism of development, being determined by suppression of normal hematopoiesis which can be explained by following mechanisms:
* Intense consumption by leukemic blast cells of substances compulsory for normal erythrocytopoiesis (folate, B12 etc..)
* Decreased proliferative activity of erythroid cells in the bone marrow because blast leukemic cells inhibits normal erythropoiesis;
* Leukemic cells stimulate synthesis of anti-erythrocyte antibodies and killer T lymphocyte T – intensification of hemolysis;
* In leucosis there can be found as well blood hypocoagulability, determined by thrombocytopenia, anemia as well as by changed hemostatic abilities of thrombocytes, all these being induced by leukemic cells.
* *Malaise, fatigability* which are explained by anemic syndrome;
* *Bone pain and tenderness on palpation* – subperiosteal bone infiltration, bone marrow expansion and bone resorption;
* *Headache, nausea, vomiting, papilledema, seizures, c*oma – explained by leukemic infiltration of CNS;
* *Abdominal discomfort* – explained by generalized lymphadenopathy, splenomegaly, hepatomegaly due to leukemic infiltration of these organs;
* *Increased vulnerability to infections* – explained by immaturity of white cells and ineffective immune function; *neutropenia* with neutrophil count below 500 neutrophils/μL
* *Leukostasis* – a condition in which circulating blast cell count is markedly elevated (100 000 blast cells/ μL), these increasing blood viscosity and predispose to development of leukoblastic emboli which can obstruct small vessels in the pulmonary as well as cerebral circulation. Cerebral leukostasis is characterised by diffuse headache, vomiting, lethargy and often progress to cerebral coma. Pulmonary leukostasis is characterised by progressive dyspnea.
* *Hyperuricemia and other metabolic disorders* – explained by abnormal proliferation and metabolism of leukemic cells. There is characteristic increased breakdown of purine nucleotides secondary to leukemic cell death (also can be the result of chemotherapy).

**Acute leucosis**

Acute leucosis represents very severe (malign) forms with predominance in the bone marrow of atypical blast cells. According to blast cells which predominate in the bone marrow and are released in peripheral blood, as well as according to cytochemical particularities of these cells, acute leucosis can be classified in:

* myeloblast acute leucosis;
* lymphoblast acute leucosis;
* promyelocytic acute leucosis;
* monoblast acute leucosis;
* erythromyeloblast acute leucosis;
* morphologically and cytochemically non-differentiated acute leucosis

**Myeloblast acute leucosis** (**acute myeloid leukemia)**

*Acute myeloid leukemia* (AML) is a tumor of hematopoietic progenitors caused by acquired oncogenic mutations that impede differentiation, leading to the accumulation of immature myeloid blasts in the marrow. The arrest in myeloid development leads to marrow failure and complications related toanemia, thrombocytopenia, and neutropenia. AML occurs at all ages, but the incidence rises throughoutlife, peaking after 60 years of age. Is the most frequent form of leucosis in adults. There are about 13,000 new cases each year in the United States.AML is quite heterogeneous, reflecting the complexities of myeloid cell differentiation.

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**Fig. 1 Acute myeloid leukemia without maturation**

Myeloblasts have delicate nuclear chromatin, prominent nucleoli, and fine azurophilic granules in the cytoplasm. **B**, In the flow cytometric analysis shown, the myeloid blasts, represented by the red dots, express CD34, a marker of multipotent stem cells, but do not express CD64, a marker of mature myeloid cells. **C**, The same myeloid blasts express CD33, a marker of immature myeloid cells, and a subset express CD15, a marker of more mature myeloid cells. Thus, these blasts are myeloid cells showing limited maturation. *(From Robbins-Cotran; Pathologic basis of disease)*

Most patients present within weeks or a few months of the onset of symptoms with complaints related to anemia, neutropenia, and thrombocytopenia, most notably fatigue, fever, and spontaneous mucosal andcutaneous bleeding. Thrombocytopenia results in a bleeding diathesis, which is often prominent. Cutaneous petechiae and ecchymoses, serosal hemorrhages into the linings of the body cavities and viscera, and mucosal hemorrhages into the gingivae and urinary tract are common. Procoagulants and fibrinolytic factors released by leukemic cells exacerbate the bleeding tendency. Infections are frequent, particularly in the oral cavity, skin, lungs, kidneys, urinary bladder, and colon, and are often caused by opportunists such as fungi, *Pseudomonas*, and commensals. Signs and symptoms related to involvement of tissues other than the marrow are usually less striking in AML than in acute lymphoblastic leukemia, but tumors with monocytic differentiation often infiltrate the skin (leukemia cutis) and the gingiva; this probably reflects the normal tendency of monocytes to extravasate into tissues. Central nervous system spread is less common than in acute lymphoblastic leukemia. AML occasionally presents as a localized soft-tissue mass known variously as a myeloblastoma, granulocytic sarcoma, or chloroma. Without systemic treatment, such tumors inevitably progress to full-blown AML over time. In this form of leucosis in the blood there are found very young granulocytes (myeloblasts) and mature segmented granulocytes, meantime intermediary cells like promyelocytes, myelocytes and metamyelocytes are lacking – so called “*hiatus leukemicus*”. AML is a difficult disease to treat. About 60% of patients achieve complete remission with chemotherapy, but only 15% to 30% remain free of disease for 5 years. AML of all types are treated with bone marrow transplantation when possible.

**Acute lymphoblastic leukemia** (ALL) are neoplasms composed of immature B (pre-B) or T (pre-T) cells, which are referred to as lymphoblasts. About 85% are B-ALLs, which typically manifest as childhood acute leukemias. The less common T-ALLs tend to present in adolescent males as thymic ―lymphomas There is, however, considerable overlap in the clinical behavior of B- and T-ALL; for example, B-ALL uncommonly presents as a mass in the skin or a bone, and many T-ALLs present with or evolve to a leukemic picture. Because of their morphologic and clinical similarities, the various forms of ALL will be considered together. ALL is the most common cancer of children. Approximately 2500 new cases are diagnosed each year in the United States, most occurring in individuals under 15 years of age. ALL is almost three times as common in whites as in blacks, and slightly more frequent in boys than in girls. Hispanics have the highest incidence of any ethnic group. B-ALL peaks in incidence at about the age of 3, perhaps because the number of normal bone marrow pre-B cells (the cell of origin) is greatest very early in life. Similarly the peak incidence of T-ALL is in adolescence, the age when the thymus reaches its maximal size. Band T-ALL also occur less frequently in adults of all ages.



**Fig 2. Acute lymphoblastic leukemia**.

Lymphoblasts with condensed nuclear chromatin, small nucleoli, and scant agranular cytoplasm. **B** and **C** represent the phenotype of the ALL shown in **A**, analyzed by flow cytometry. **B**, Note that the lymphoblasts represented by the red dots express terminal deoxynucleotidyl-transferase (TdT) and the B-cell marker CD22. **C**, The same cells are positive for two other markers, CD10 and CD19, commonly expressed on pre-B lymphoblasts. Thus, this is a B-ALL (From Robbins-Cotran; Pathologic basis of disease).

It should be emphasized that although ALL and AML are genetically and immunophenotypically distinct, they are clinically very similar. In both, the accumulation of neoplastic blasts in the bone marrow suppresses normal hematopoiesis by physical crowding, competition for growth factors, and other poorly understood mechanisms. The common features and those more characteristic of ALL are the following:

**•** Abrupt stormy onsetwithin days to a few weeks of the first symptoms

**•** Symptoms related to depression of marrow function, including fatigue due to anemia; fever, reflecting infections secondary to neutropenia; and bleeding due to thrombocytopenia

**•** Mass effects caused by neoplastic infiltration(which are more common in ALL), including bone pain resulting from marrow expansion and infiltration of the subperiosteum; generalized lymphadenopathy, splenomegaly, and hepatomegaly; testicular enlargement; and in T-ALL, complications related to compression of large vessels and airways in the mediastinum

**•** *Central nervous system manifestations* such as headache, vomiting, and nerve palsies resulting from meningeal spread, all of which are also more common in ALL

**Promyelocytic acute leucosis** – in the bone marrow there can be found atypical cells and huge number of atypical promyelocytes and myelocytes. Cytoplasm of these cells is rich in violet-brown granulation, localised also on the nucleus. These granulations contain acid mucopolysaccharides. Cells in this form of leucosis have a high number of lysosomes. Cytochemically there is positive reaction to peroxidase, acid phosphatase, lipids and non-specific esterase. Glycogen in the cytoplasm is spread diffusely.

**Monoblast acute leucosis** – is a rare form, there are little differences from myeloblast acute leucosis. In the peripheral blood of patients with this form of leucosis there is high count of young granulocytes. Blastic cells have many nucleoli in the nucleus. Cytochemically can be identified by positive reaction to peroxidase, acid phosphatase, non-specific esterase.

**Acute erythromyeloblast leucosis** – is characterised by hyperplasia of cells from erythroid lineage without evident signs of hemolysis. Blastic cells have origin from myelopoietic cell. In the peripheral blood there is found normo- or- hyperchromic anemia without reticulocytosis, leucocytopenia and thrombocytopenia.

**Chronic leucosis**

Chronic leucosis have a relatively benign evolution, cellular mass being formed from differentiated cells from all stages of maturation, with partial maturation suppression. Accumulation of cells from different maturation stages denotes a longer and more persistent monoclonal stage in chronic leucosis. According to type of cells found in peripheral blood there can be distinguished following types of chronic leucosis:

* myeloid chronic leucosis;
* lymphoid chronic leucosis;
* monocytic chronic leucosis;
* megakaryocytic chronic leucosis;
* chronic erythromyelosis;
* erythremia

**Chronic myeloid leukemia *(CML***)

CML is primarily a disease of adults but also occurs in children and adolescents. The peak incidence is in the fifth to sixth decades of life. There are about 4500 new cases per year in the United States. The onset is insidious. Mild-to-moderate anemia and hypermetabolism due to increased cell turnover lead to fatigability, weakness, weight loss, and anorexia. Sometimes the first symptom is a dragging sensation in the abdomen caused by splenomegaly, or the acute onset of left upper quadrant pain due to splenic infarction. The natural history is one of slow progression; even without treatment, the median survival is about 3 years. After a variable period averaging 3 years, about 50% of patients enter an accelerated phase marked by increasing anemia and thrombocytopenia, sometimes accompanied by a rise in the number of basophils in the blood. Additional clonal cytogenetic abnormalities, such as trisomy 8, isochromosome 17q, or duplication of the Ph chromosome, often appear. Within 6 to 12 months, the accelerated phase terminates in a picture resembling acute leukemia (*blast crisis*). In the other 50% of patients, blast crises occur abruptly without an accelerated phase. In 70% of crises, the blasts are of myeloid origin (myeloid blast crisis), whereas in most of the remainder the blasts are of preŔB cell origin (lymphoid blast crisis).



**Fig.3 Chronic myeloid leukemia**

Peripheral blood smear shows many mature neutrophils, some metamyelocytes, and a myelocyte

(From Robbins-Cotran; Pathological basis of disease)

This is taken as evidence that CML orginates from a pluripotent stem cell with both myeloid and lymphoid potential. Recently, it has been observed that in greater than 85% of cases CML is associated with the appearance of mutations that interfere with the activity of Ikaros, a transcription factor that regulates the differentiation of hematopoietic progenitors. The same types of Ikaros mutations are also seen in BCR-ABL-positive ALL, suggesting that these two varieties of aggressive leukemia have a similar pathogenic basis.

**Chronic lymphocytic leukemia (CLL)**

CLL is the most common leukemia of adults in the Western world. There are about 15,000 new cases of CLL each year in the United States. The median age at diagnosis is 60 years, and there is a 2:1 male predominance. CLL is much less common in Japan and other Asian countries than in the West.



**Fig.4 Chronic lymphocytic leukemia**

This peripheral blood smear is flooded with small lymphocytes with condensed chromatin and scant cytoplasm. A characteristic finding is the presence of disrupted tumor cells (smudge cells). A coexistent autoimmune hemolytic anemia explains the presence of spherocytes (hyperchromatic, round erythrocytes). A nucleated erythroid cell is present in the lower left-hand corner of the field. In this setting, circulating nucleated red cells could stem from premature release of progenitors in the face of severe anemia, marrow infiltration by tumor (leukoerythroblastosis), or both (From Robbins-Cotran; Pathologic basis of diseases).

In the peripheral blood there is a considerable number of lymphocytes, can be present single prolymphocytes as well as lymphoblasts. Often, on blood smear there are found so-called *Gumpreht s*hade – traces of lymphocytes nuclei destroyed during smear preparation. Bone marrow morphologically is characterised by diffuse of focal growth of lymphocytes.

Patients are often asymptomatic at diagnosis. When symptoms appear, they are nonspecific and include easy fatigability, weight loss, and anorexia. Generalized lymphadenopathy and hepatosplenomegaly are present in 50% to 60% of symptomatic patients. The leukocyte count is highly variable; leukopenia can be seen in individuals with SLL and marrow involvement. CLL disrupts normal immune function through uncertain mechanisms. Hypogammaglobulinemia is common and contributes to an increased susceptibility to infections, particularly those caused by bacteria. Conversely, 10% to 15% of patients develop hemolytic anemia or thrombocytopenia due to autoantibodies made by non-neoplastic B cells. The course and prognosis are extremely variable and depend primarily on the clinical stage. Overall median survival is 4 to 6 years, but over 10 years in individuals with minimal tumor burdens at diagnosis. Patients are generally treated with gentle chemotherapy to control symptoms. Bone marrow transplantation is being offered to the relatively young.

**Chronic monocyte leucosis** is characterised by tumoral process with high number of monocytes in the bone marrow and peripheral blood. In peripheral blood smear, beside mature monocytes there are found as well erythrocariocytes and single promonocytes. Characteristic sign of this chronic leucosis is high level of lysosim in the blood and urine, as well as positive reaction to non-specific esterase.

**Chronic erythromyeloid leucosis** is characterised by a tumoral process with bone marrow hyperplasia, presence in the peripheral blood of erythrocariocytes, sometimes there can be found promyelocytes, myelocytes, erythroblasts and myeloblasts. There is also present a normochromic anemia with moderate increased reticulocyte count in peripheral blood. In spleen aspirate, there are signs of metaplasia and increased number of erythrocariocytes. For this form of chronic leucosis there is characteristic positive reaction to acid phosphatase.

**Chronic megakaryocytic leucosis** represents a tumoral process which involve predominatlly megakaryocytic lineage of bone marrow. In peripheral blood there is hyper-thrombocytosis (800 000 – 1 000 000 thrombocytes/mm3), basophilia and distorted thrombocytes. Sometimes in the liver can be present myeloid and megakaryocyte infiltration.

**Chronic myeloid unidentified leucosis** – a group of chronic leucosis which cannot be identified specifically. In these forms of leucosis is characteristic myeloid polymorphocellular hyperplasia of bone marrow and basophilia, which mechanism is still unknown.

**Lymphomas**

Lymphomas represent a group of tumors characterised by local blastomatous proliferation of lymphoid tissue, especially at the level of lymphatic nodes, where T and B lymphocytes undergo differentiation and proliferation as they interact with antigen. These represent solid tumors which are composed of neoplastic lymphoid cells. Clinical picture of lymphomas are dominated by manifestations related to uncontrolled lymph node and lymphoid tissue growth, bone marrow involvement and constitutional symptoms (fever, fatigue, weight loss, night sweats, chills) related as well to rapid growth of abnormal lymphoid cells and tissues.

There are recognized Hodgkin and non-Hodgkin lymphomas.

**Hodgkin lymphomas** (HL) in past also known as Hodgkin disease (*lymphogranulomatosis*), is a specialized form of lymphoma characterised by presence of abnormal characteristic cells – *Reed-Sternberg* cells (cells with mirror-image nuclei and large eosinophilic nucleoli). Etiology of Hodgkin lymphomas is largely unknown, although there is speculated exposure to some viruses and carcinogens. Hodgkin lymphoma accounts for 0.7% of all new cancers in the United States; there are about 8000 new cases each year. The average age at diagnosis is 32 years. It is one of the most common cancers of young adults and adolescents, but also occurs in the aged. It was the first human cancer to be successfully treated with radiation therapy and chemotherapy, and is curable in most cases.

Hodgkin lymphoma encompasses a group of lymphoid neoplasms that differ from NHL in several respects. While NHLs frequently occur at extranodal sites and spread in an unpredictable fashion, HL arises in a single node or chain of nodes and spreads first to anatomically contiguous lymphoid tissues. For this reason, the staging of HL is much more important in guiding therapy than it is in NHL. HL also has distinctive morphologic features. It is characterized by the presence of neoplastic giant cells called *Reed-Sternberg cells*. These cells release factors that induce the accumulation of reactive lymphocytes, macrophages, and granulocytes, which typically make up greater than 90% of the tumor cellularity. In the vast majority of HLs, the neoplastic Reed-Sternberg cells are derived from germinal center or post-germinal center B cells. The origin of the neoplastic Reed-Sternberg cells of classical HL has been explained through elegant studies relying on molecular analysis of single isolated Reed-Sternberg cells and variants. In the vast majority of cases, the Ig genes of Reed-Sternberg cells have undergone both V(D)J recombination and somatic hypermutation, establishing an origin from a germinal center or post-germinal-center B cell. Despite having the genetic signature of a B cell, the Reed-Sternberg cells of classical HL fail to express most B cell specific genes, including the Ig genes. The cause of this wholesale reprogramming of gene expression has yet to be fully explained.

Activation of the transcription factor NF-κB is a common event in classical HL. NF-κB is activated either by EBV infection or by some other mechanism and turns on genes that promote lymphocyte survival and proliferation. EBV+ tumor cells express latent membrane protein-1 (LMP-1), a protein encoded by the EBV genome that transmits signals that up-regulate NF-κB. Activation of NF-κB also occurs in EBV- tumors, in some instances as a result of acquired mutations in IκB, a negative regulator of NF-κB. It is hypothesized that activation of NF-κB by EBV or other mechanisms rescues crippled germinal-center B cells that cannot express Igs from apoptosis, setting the stage for the acquisition of other unknown mutations that collaborate to produce Reed Sternberg cells. Little is known about the basis for the morphology of Reed-Sternberg cells and variants, but it is intriguing that EBV infected B cells resembling Reed-Sternberg cells are found in the lymph nodes of individuals with infectious mononucleosis, strongly suggesting that EBV-encoded proteins play a part in the remarkable metamorphosis of B cells into Reed-Sternberg cells. The florid accumulation of reactive cells in tissues involved by classical HL occurs in response to a wide variety of *cytokines* (such as IL-5, IL-10, IL-13, and TGF-β) and *chemokines* (such as TARC, MDC, IP-10, and CCL28) that are secreted by Reed-Sternberg cells. Once attracted, the reactive cells produce factors that support the growth and survival of the tumor cells and further modify the reactive cell response. For example, eosinophils and T cells express ligands that activate the CD30 and CD40 receptors found on Reed-Sternberg cells, producing signals that up-regulate NF-κB.

HL most commonly present as painless lymphadenopathy. Patients with the nodular sclerosis or lymphocyte predominance types tend to present with stage IŔII disease and are usually free of systemic manifestations. Patients with disseminated disease (stages IIIŔIV) or the mixed-cellularity or lymphocyte depletion subtypes are more likely to have constitutional symptoms, such as fever, night sweats, and weight loss. Cutaneous anergy resulting from depressed cell-mediated immunity is seen in most cases. The mix of factors released from Reed-Sternberg cells suppress TH1 immune responses and may contribute to immune dysregulation.

The spread of HL is remarkably stereotyped: nodal disease first, then splenic disease, hepatic disease, and finally involvement of the marrow and other tissues. Because of this behavior, radiation therapy can be curative for persons with early-stage disease. Thus, the staging of HL not only determines the prognosis, but also guides therapy. Staging involves physical examination, radiologic imaging of the abdomen, pelvis, and chest, and biopsy of the bone marrow. Systemic treatment is preferred whenever the staging is equivocal.

**Non-Hodgkin lymphomas** represent a group of heterogenous lymphocytic cancer which can spread to various tissues throughout the body, including the bone marrow. This can be either B - or T– cell neoplasm, the etiology of which is largely unknown. but it was remarked that Non-Hodgkin lymphoma are seen with increased frequency in people with HIV, individuals who received chronic immunosuppressive therapy, after organ transplantation, persons with acquired or inherited immunodeficiencies.

Although Non-Hodgkin lymphoma can originate in any of the lymphoid tissue in the body, most commonly originate in the lymph nodes (most often are involved retroperitoneal, mesenterial and pelvic lymph nodes). B-cell lymphomas tend to proliferate in B-cell areas of the lymph node, whereas T-cell lymphomas typically grow in paracortical T-cell area of lymph nodes. Non-Hodgkin lymphomas have potential to spread to any of lymphoid tissue throughout the body, especially the liver, spleen and bone marrow. Frequently in these patients there is increased susceptibility to infections (bacterial, viral and fungal), hypogammaglobulinemia and poor humoral response.

There are two most frequent forms:

*Lymphocytomas* – tumors which consist from prolymphocytes and mature lymphocytes which have origin from T and B population of lymphocytes. Tumor has an identical structure like lymph node. Lymphocytomas are considerd benign tumors.

*Lymphosarcomas* – are malign tumors, which consist from blast cells of lymphoid lineage (lymphoblasts and prolymphoblasts).