

neutropenia of medium severity. In some patients with rheumatoid arthritis severe form of neutropenia with splenomegaly and high levels of rheumatic factors (Felty's syndrome) occur.

Neutropenia may develop in bacterial, viral, parasitic, rickettsial diseases. Abnormal production, margination or utilization of neutrophils may be involved. In infectious mononucleosis, infectious hepatitis and HIV infection the neutrophil production is impaired. In influenza and in rickettsial infections increased neutrophil margination occurs. In gram-positive infections the utilization of neutrophils is elevated. Neutropenia may develop in splenomegaly due to hypersplenism owing to the increased uptake of neutrophils in the spleen.

**Lymphocytopenia** (lymphopenia) is a condition the count of lymphocytes in  $1 \mu\text{l}$  of blood falls to less than 1500 in adults and to 3000 in young people and children.

It occurs most commonly in congenital immunodeficiency syndrome. It is observed also following irradiation, cytotoxic and corticosteroid treatment. Lymphopenia accompanies the lymphomas, aplastic anaemia, renal failure, right cardiac failure, and cachexia.

**Monocytopenia** appears in acute infections, in stress and following glucocorticoid application. It is developing in aplastic anaemia, acute myeloid leukaemia, after myelotoxic, immunosuppressive treatment.

**Eosinopenia** occurs in stress, infections and following glucocorticoid application.

**Eosinophilia** can appear during chronic myeloid leukaemia. It may be severe in parasitic and allergic diseases. The underlying causes of eosinophilia are usually chronic inflammatory and malignant diseases.

In idiopathic hypereosinophilic syndrome there is hepatosplenomegaly, peripheral neuropathy, and congestive heart failure.

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## 2.7 Malignant haematologic diseases

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The haematologic malignancies comprise a group of conditions originating in bone marrow and lymphatic glands. Primary bone marrow diseases are the leukaemias, the immunoproliferative and the myeloproliferative syndromes. It is evident in all these diseases, that the origin lies in cell mutation being the basis for development of malignant clone. The malignant clone exhibits an abnormal growth potency. In chronic lymphocytic leukaemia the malignant lymphocytes produce an identical immunoglobulin. In chronic myelogenous leukaemia all cells of myeloid series, the erythroid precursors, the megakaryocytes and B lymphocytes have an identical Ph<sup>1</sup> Philadelphia chromosome. Many further facts indicate that the malignant cells arise from one cell and by their expansion the clone of malignant cells is formed.

### 2.7.1 Myeloproliferative disorders

Four diseases may be included in this group, each of them being an independent clinical unit:

1. Polycythaemia vera
2. Myelofibrosis with myeloid metaplasia
3. Essential thrombocytopenia
4. Chronic myelogenous leukaemia

In all these conditions are an uncontrolled expansion of bone marrow elements included. Increase in erythroid, myeloid and megakaryocyte cells production is due to malignant transformation of pluripotent stem cell. Fibrosis of bone marrow is frequently present owing to growth stimuli affecting normal fibroblasts. The origin of these growth stimuli is in neoplastic cells. They are produced most probably by megakaryocytes in bone marrow. In myeloproliferative disorders the megakaryocytes count is usually extremely elevated.

**Polycythaemia vera** is a myeloproliferative neoplastic disease. The stem erythroid cell is primarily affected. Hyperplasia of all bone marrow components

is usually observed however the raise in erythroid precursors is dominant. The enhanced erythrocyte production is completely autonomous. Any stimulus is not present like hypoxia or enhanced erythropoietin production, which could be responsible for increase in erythrocyte production. In polycythaemia vera rise the values of haematocrit. If haematocrit above 54 per cent in men or above 50 per cent in women is stated it is necessary to look for the cause of this increase. Important is to know if there is increase in absolute account of erythrocytes or if the volume of plasma is not falling. Information above the erythrocyte mass provides the method performed with erythrocytes labeled by  $^{51}\text{Cr}$ .

In polycythaemia vera are leucocyte and thrombocyte values usually increased. In other myeloproliferative disorders polycythaemia may be present. The underlying cause of polycythemia vera is not known. The patients are sometimes without difficulties. Difficulties originating in hypervolaemia, hyperviscosity and thrombocyte dysfunction appear. These alterations represent a severe risk of myocardial infarction development and of venous thromboembolism. Enhanced cell formation and destruction leads to hyperuricaemia. Increase in basophil production enables the enhancement of histamin release, manifested by severe itching.

The confirmation of polycythaemia vera is not easy. But, erythropoietin is usually not increased. In few per cent of affected patients develops acute leukaemia. The leukaemia appears more frequently in patients treated by cytostatics for polycythaemia than in untreated patients. The bone marrow fibrosis may develop in polycythaemia to such a degree that the erythrocyte production is reduced. As consequens the anaemia and extramedullar haemopoiesis with splenomegaly is present.

**Relative polycythaemia** (false polycythaemia, stress polycythaemia). This condition occurs in obese persons, in hypertension or in chronic stress. The haematocrit values are usually 55 to 60 per cent. The mass of erythrocytes is normal and the volume of plasma is decreased. The causes of this condition are not completely understood.

**Absolute polycythaemia.** This condition can be due to enhanced erythrocyte production like in polycythaemia vera. In this case we could speak about primary absolute polycythaemia. The production may raise however owing to the stimuli of physiolog-

ical character. This type of absolute polycythaemia (secondary) occurs in conditions associated with hypoxia of tissues. This condition occurs frequently during insufficient saturation of blood with oxygen. Hypoxia induces increase in erythropoietin production in kidneys. Erythropoietin stimulates the erythroid precursors and the erythrocyte production which should provide tissues with oxygen. Increased erythrocyte production and larger erythrocyte mass will be however manifested by **increased blood viscosity** what actually causes that the oxygen supply in tissues does not increase. This state develops e.g. in patients with congenital cyanotic heart diseases and in patients with pulmonary diseases. If the haematocrit values are more than 75 per cent, the venepunction remains the only intervention to decrease the volume of circulating blood. The erythrocytic mass loss, however, will be soon restituted. Every haematocrit elevation is very unfavorable condition. **Causing the viscosity elevation it diminishes the blood flow through the brain, reduces the heart volume and forms favorable conditions to thrombosis development.**

**Myelofibrosis and myeloid metaplasia** is a myeloproliferative disorder with expansion of all cell types in bone marrow, due to pluripotent stem cell malignant deformation. The bone marrow fibrosis is a response to the expansion and malignant transformation. In advanced stage may fibrosis occupy the whole space in bone marrow. The extramedullar haemopoiesis in the liver and the spleen with hepatomegaly and splenomegaly becomes the cardinal symptom of disease. The extramedullar haemopoiesis is the picture of reactivation of fetal sites of haemopoiesis, or it is due to bone marrow stem cell migration.

Clinical manifestation of myelofibrosis with myeloid metaplasia need not to be marked. In the peripheral blood are erythrocytes with nuclei observed. They are the sign of extramedullar haemopoiesis. Leukocytosis with the shift to the left is found. Myelofibrosis with myeloid metaplasia (MMM) can progress very slowly. Splenomegaly, hepatomegaly and anaemia with thrombocytopenia are developing. The splenomegaly may attain an extreme degree and may lead to portal hypertension. These alterations prevail frequently in the clinical pattern. In treatment of progressive anaemia is to consider the iron and folic acid supplementation or transfusion. The splenectomy solves only the problemes

connected with enhanced pressure symptoms in the abdominal cavity.

**Essential thrombocytaemia** is a myeloproliferative disorder, dominant sign of which is the elevated thrombocyte count (above 1 000 000 in  $1\mu\text{l}$ ). Main symptoms of this condition are due to thrombosis or to haemorrhage. Nevertheless, the patients may be without troubles. Acral pain can appear sometimes due to thrombosis in microcirculation and is manifested by gangrene of toes. The thrombocyte agregability inhibition by acetylsalicylic acid is used to suppress the thrombus appearance in microcirculation.

## 2.7.2 Leukaemias

**Leukaemia is a condition where the bone marrow is replaced by malignant clone of lymphocytes, monocytes or granulocytes, resp. of plasmocytes and erythrocytes. The immature cells are released into the peripheral blood.** The progress may be chronic or explosive. When the leukaemias are not treated they end always lethally.

**Lymphomas are tumors arising from cells of lymphatic system.** The bone marrow in lymphomas can be infiltrated by lymphoid cells, nevertheless is very seldom the site of origin of primary lymphomas.

### 2.7.2.1 Chronic leukaemias

**The chronic myeloid leukaemia (CML)** is frequently classified as myeloproliferative disorder because of evident **expansion of all bone marrow cell types**, which all have the Philadelphia chromosome indicating the pluripotent stem cell mutation as the initial alteration. The Philadelphia chromosome represents the long branch part of chromosome 22 translocation to chromosome 9. This translocation can be the underlying cause of cellular oncogenes activation.

CML appears in adults of age between 40 to 50 years. Sometimes it appears also in children. Patients need not have findings about the exposure to effects of carcinogenes or radioactivity in their personal medical history. Following explosion of atomic bombs in Hiroshima and Nagasaki the number of patients with CML raised significantly in 7 years in persons who survived the catastrophe outside of epicentre.

In patients with CML the leukocytosis and presence of myeloid precursors in peripheral blood are

found. In the initial stage is splenomegaly usually present, often with thrombocytosis. During periodic oral chemotherapy anaemia occasionally with thrombocytosis appear following 3 to 5 years of treatment duration. Patients use to have fever and weakness. In peripheral blood promyelocytes and myeloblasts occur. This stage is named the blastic phase.

A promising therapeutic strategy is the application of human alpha interferon which may induce disease remission and suppress the Philadelphia chromosome.

**Chronic lymphocytic leukaemia (CLL).** This condition is named also the accumulative disease of immunologically incompetent small lymphocytes. It occurs more frequently in men than in women. In peripheral blood is absolute lymphocytosis. Lymphocytosis is permanent and reaches values above  $15 \times 10^9/l$  of lymphocytes. The bone marrow is hypercellular. More than 40 per cent of all cells in bone marrow are the lymphocytes. In the peripheral blood in the bone marrow too prevail the small mature lymphocytes. In blood smears typical Gumprecht's shadows are present. Owing to the neoplastic lymphocyte accumulation the spleen and the liver become slowly enlarged. The lymphocytes are immunologically incompetent. Therefore hypogammaglobulinaemia and predisposition to infections are present.

**The lymphocytes in chronic lymphocytic leukaemia are clonic proliferation of B lymphocytes.** The surface immunoglobulins are the IgM and IgD. The proliferation of T lymphocytes is found in only 1 per cent of patients with CLL. The etiology of CLL is not known. The course of disease is typical. In the 0 stage only lymphocytosis is present. In the first and second stages tumors (of lymphatic glands, liver and spleen) appear. In further stages: third and fourth anaemia and thrombocytopenia appear due to bone marrow suppression. The splenomegaly is the underlying cause of hypersplenism (erythrocyte and thrombocyte sequestration).

**Leukaemic reticuloendotheliosis** (hairy cell leukaemia – HCL) is a neoplastic disorder with typical hairy cells in peripheral blood and bone marrow. The hairy cells are similar to the lymphocytes with thin projections. The course of disease may be leukaemic or aleukaemic with very slow development. Pancytopenia and splenomegaly dominate in the clinical pattern. The deoxyformycin treatment can result in complete haematologic remission in some patients.

The most preferal treatment of first choice remains the splenectomy.

### 2.7.2.2 Acute leukaemias

**In acute leukaemias the immature haematopoietic cells proliferate without differentiation to normal mature blood cells.** The normal erythrocyte, granulocyte and thrombocyte production is limited by myeloblast or lymphoblast proliferation. This leads to the clinical manifestation of disease. Anaemia, reduced resistance to infections and bleeding are observed. Irradiation damage, viral infections, genetic predisposition or exposition to effects of some chemical agents (substances) is frequently stated in the medical history of patient. The precise mechanism of action of these factor, or their interaction with normal stem cells is not known. It is not understood how the production of malignant clone arise under their influence. Acute leukaemias are classified into two large groups:

1. Acute lymphoblastic leukaemia (ALL)
2. Acute myeloblastic leukaemia (AML)

The ALL occurs primarily in children, the AML, on the other hand, occurs primarily in adults. About 20 per cent of acute leukaemias appear in adults, however those are of lymphoblastic type. Precise determination of leukaemia type is important regarding the treatment. It is performed on the basis of histological examination of bone marrow, histochemical examination of leucocytes and of surface cytoplasmic markers. The chromosomal alterations in acute leukaemia correlate with certain type of cells. There is e.g. a subgroup of patient with atypical ALL with cells containing the Philadelphia chromosome. In despite of a considerable heterogeneity acute leukaemias are classified into following subgroups.

#### Acute myeloblastic leukaemias:

- M<sub>1</sub> – acute myeloblastic leukaemia without differentiation of blasts  
 M<sub>2</sub> – acute myeloblastic leukaemia with differentiation (especially of myeloblasts and promyelocytes)  
 M<sub>3</sub> – acute promyelocytic leukaemia (with prevalence of abnormal promyelocytes)  
 M<sub>4</sub> – acute myelomonocytic leukaemia (with cells

having myeloid and monocytic signs)

M<sub>5</sub> – acute monocytic leukaemia (monoblasts with abundant cytoplasm)

M<sub>6</sub> – erythroleukaemia

M<sub>7</sub> – acute megakaryocytic leukaemia

#### Acute lymphoblastic leukaemias:

L<sub>1</sub> – with predominant population of small cells with small nuclei

L<sub>2</sub> – acute leukaemia with heterogenous group of cells with various size and nucleus form

L<sub>3</sub> – acute leukaemia with homogenous cell population similar to the Burkitt's lymphoma

Single subgroups are characterized not only by (the) morphologic finding in blood samples but by more or less typical clinical pattern. In promyelocytic leukaemia M<sub>3</sub>, e.g., the disseminated intravascular coagulation frequently occurs. The promyelocytes release enzymes from their granules stimulating the coagulation cascade and facilitate the intravascular coagulation. The acute monocytic leukaemia – M<sub>5</sub> is usually associated with skin and oral mucosa infiltration with leukaemic cells. The lymphoblastic leukaemia of L<sub>1</sub> subtype occurs above all in children and the subtype L<sub>2</sub> in adults. L<sub>3</sub> – has an unfavourable prognosis.

**Acute leukaemia is clinically manifested by outstanding symptoms.** Infections are observed owing to the impaired function of bone marrow leading to granulocytopenia. Bleeding due to thrombocytopenia and anaemia caused by disorders of erythroid maturation. Bone pain may occur due to the leukaemic marrow expansion. In ALL splenomegaly and lymphadenopathy are frequently present. The global lymphocyte count is usually elevated. It may be sometimes more than 100 000 lymphocyte in 1  $\mu$ l of blood. In aleukaemic form nevertheless it can be less than 3 000 in 1  $\mu$ l. Analysis of the blood smears reveals pathologic finding almost regularly. Some leucocytes are mature a great part however is on the level of blasts. In the peripheral blood single forms of development are present. The uneven blood cell (of various differentiation degree) distribution is termed hiatus leukaemicus. Values of haemoglobin, counts of erythrocytes and thrombocytes use to be reduced. Uric acid level is usually elevated due to the excessive production and desintegration of leucocytes. The hyperuricaemia leads to the renal damage. The bone

marrow examination reveals almost in every case the hypercellularity and cells without differentiation replacing of the normal bone marrow.

**Acute leukaemia is always an urgent condition.** Decision on further treatment should be made considering the global findings and the severity of the state. If the leucocyte count is higher than 100 000 in  $1 \mu\text{l}$  the patient is treated with cerebral haemorrhage usually due to leukostasis. High count of leucocytes, especially the presence of rigid blasts produce an obturation plug (stopper). The therapeutic reduction of leucocyte count elevates the uric acid level. The patient is threatened with infections particularly when the granulocytes in circulation are lacking or there are only very few of them. The whole blood transfusion leads to haemoglobin, erythrocyte and thrombocyte count rise. It is prevention of haemorrhagia. The cytostatic treatment is used with intention to stop the proliferation of cells. The drugs act in various phases of cell cycle. The bone marrow transplantation is to be considered preferentially in young patients respecting a suitable donor regarding the HLA. For bone marrow transplantation are suitable candidates those patients in whom following the initial treatment complete remission occurred. The bone marrow transplantation presents a risk of infection, haemorrhagic complications and interstitial pneumonia. Bone marrow aplasia may appear later. The leukaemic clone is eradicated by cytotoxic drugs before transplantation. Reappearing of leukaemia can be due to insufficient eradication of leukaemic clone or to the transferrable agent transition into the new cell line. A perspective hopeful therapeutic possibility are the monoclonal antibodies against the surface antigens of leukaemic cells.

### 2.7.3 Myelodysplastic syndrome

On the contrary to acute leukaemia the **myelodysplastic syndromes are characterized by slow development ending in anaemia refractory to the standard treatment.** The affected patients are usually elderly people. In younger people may the myelodysplastic syndromes develop following radiotherapy combined with antineoplastic chemotherapy of diseases like m. Hodgkin or carcinoma ovarii. At the beginning weakness and a marked decline in physical performance appear. Macrocytic anaemia is usually present in addition to leukopenia combined with thrombocytopenia or without it. The bone marrow is

hypercellular with rise in iron stores and with abnormal erythroid precursors and higher portion (participation) of immature myeloid cells. This condition is named the refractory anaemia or preleukaemia. The beginning and course is usually rather variable. These conditions therefore are classified in five types of myelodysplastic syndromes:

1. Refractory anaemia
2. Refractory anaemia with sideroblasts
3. Refractory anaemia with rise in blast count
4. Chronic myelomonocytic leukaemia
5. Refractory anaemia with transformation

The risk of acute leukaemia development increases with rise of blast number in bone marrow. The primary treatment is directed to improvement of anaemia. Application of high vitamin B<sub>6</sub> doses has been successful in some patients.

### 2.7.4 Lymphomas

**The lymphomas form a group of malignant diseases arising from lymphatic glands or from extralymphatic tissue.** Regarding the pathologic and clinical pattern this group of malignant diseases is heterogeneous. Two large subgroups are represented by Hodgkin's disease and the non-Hodgkin's lymphomas. In both these subgroups is the enlargement of lymphatic glands the most frequent clinical sign. It should be excluded at the very beginning, if an ordinary enlargement of lymphatic glands is involved, observed in various local or generalized infections. Bioptic examination of lymphatic glands is performed subsequently.

#### 2.7.4.1 Hodgkin's disease

This condition occurs most frequently in young persons, but it can appear also in children or in older people. Asymptomatic lymphadenopathy is usually observed in patients. A lymphadenopathy accessible by aspection and palpation may be involved, however a mediastinal lymphadenopathy may be observed in X-ray examination. Fever and night sweats, weight loss, cough and itching are present in some patients.

From clinical point of view is Hodgkin's disease classified in subtypes A and B according to present

symptoms. Four histopathologic subtypes are the following: **nodular sclerosis; type with lymphocyte predominance; mixed type and lymphocyte depleted type**. In all four types is the only pathognomic sign the presence of **Reed-Sternberg cells** confirming the diagnosis. The Reed-Sternberg cells are large cells with two or more nuclei. Each nucleus contains a nucleolus with an outstanding halo resembling the owl eyes. The progenitors of Reed-Sternberg cells are the macrophages.

Nodular sclerosis is the most frequently occurring subtype of Hodgkin's disease. In lymph nodes broad fibrotic strips are present changing the typical architecture of lymphatic nodes. In the nodes lacunar cells and dispersed Reed-Sternberg cells are found. This type of Hodgkin's disease is usually asymptomatic. The mediastinal lymph nodes are especially affected. This condition occurs more frequently in young women.

The mixed subtype of Hodgkin's disease is characterized by mixed cellularity with lymphocytes, plasmatic cells and Reed-Sternberg cells. It occurs preferentially in middle-aged men. The lymphocyte predominant subtype is usually seldom. In this condition are found enlarged lymphonodes on the neck. The prognosis of this type is very favourable. The lymphocyte – depleted subtype is also infrequent occurring in older people. It uses to be accompanied with fever, night sweats and body weight loss.

In Hodgkin's disease the stages are determined (I. to VI.) because it is important regarding the treatment. When the treatment begins in more advanced stages the prognosis is worse. Immunologic disorders due to T-cell dysfunction occur in Hodgkin's disease. In patients appear frequently herpes zoster, bacterial infections and opportune infections.

#### 2.7.4.2 Non – Hodgkin's lymphomas

The non-Hodgkin's lymphomas form a heterogeneous group of tumorous diseases arising as monoclonal proliferation from malignant cell of lymphatic origin. The underlying cause is not known as it is in Hodgkin's disease. Viruses, radiation, immunosuppression and genetic conditions should be considered. About 70 per cent of non-Hodgkin's lymphomas arise from B-lymphocytes, 20 per cent from T-lymphocytes and in 10 per cent of cases the surface signs of lymphocytes can not be detected (non-B/non-T). The subtypization can be

performed determining more accurately the involved origin of malignant cells (lymphoma from suppressor T-lymphocytes, lymphoma from helper T-lymphocytes). The T-lymphocytes may become transformed into T-immunoblasts (in vitro they can bind directly to their surface the sheep erythrocytes – forming E-rosettes). B-lymphocytes, especially those located inside the follicles of lymphatic tissue, can be transformed gradually into B-immunoblasts. Hence, the tumor lineage may originate in B-line or in T-lymphocytes. The cytologic picture of non-Hodgkin's lymphomas is very motley. Lymphomas originating in T-lymphocytes have more malignant development (course) than the lymphomas arising from B-lymphocyte lineage. Nevertheless, it is important that the lymphocytes are mobile cells passing through lymphatic vessels across the tissues. So can the lymphocytes colonize distant tissues and organs. The colonization of some tissues depends on determinants of surface membrans.

The morphological picture of non-Hodgkin's lymphomas is important regarding the malignity degree, the prognosis and the treatment strategy determination. The non-Hodgkin's lymphomas are divided into the lymphomas with low grade malignity (lymphocytic lymphoma, centrocyto-centroblastic lymphoma, immunocytic lymphoma, centrocytic lymphoma); the lymphomas with higher grade of malignity (centroblastic, lymphoblastic, and immunoblastic lymphomas).

In non-Hodgkin's lymphomas chromosomal abnormalities are more frequently observed. However any specific abnormality does not exist in comparison with e.g. the Ph1 chromosome presence in chronic myeloid leukaemia. Non-Hodgkin's lymphomas occur more frequently in persons of higher age groups. The primary focus is localized often apart of lymph node. The prognosis depends on clinical stage.

#### 2.7.5 Disorders of plasmacytes

Plasma cells disorders form a group of malignancies basis from which is a clone of cells producing the monoclonal immunoglobulin. If the production of IgM is involved the Waldenstrom's macroglobulinaemia develops. When the monoclonal immunoglobulins IgG, IgA, IgD resp. IgE are produced myeloma multiplex is developing. **The basis are the malignant plasmacytes**. Under normal conditions are the plasmacyte, in fact, specialized

B-cells (Fig. 52-3, p.). The plasma cells release, immunoglobulins and are responsible for humoral immunity under physiological conditions. Increase in monoclonal immunoglobulin is (usually) detected in about 10 per cent of cases of chronic lymphocytic leukaemia.

### 2.7.5.1 Myeloma multiplex

This malignant disease of plasma cells (plasmacytes – B-lymphocytes) **is characterized by presence of monoclonal immunoglobine or its light chains in serum and urine associated with bone destruction.** Neoplasia formed of plasmacytes or B-lymphocytes producing immunoglobulins are caused by clonal proliferation of an altered cell. **Neoplasia is diffuse or concentrated in small loci localized especially in bone marrow.** The patients affected are usually over 50 years old. Back pain is the most common complaint of patients. Middle severe anaemia and elevated values of erythrocyte sedimentation rate occur. In roentgenologic examination osteoporosis or osteolytic alteration can be observed. Renal damage may be present due to light chains Ig filtered in glomeruli and to other factors (myeloma kidney). The immunoelectrophoretic examination reveals increase in monoclonal immunoglobulin values (e.g. of IgG<sup>k</sup>). Levels of other immunoglobulin types are lowered. Free, light chains kappa or lambda (Bence Jones protein) are increased and occur in urine, detectable by immunoelectrophoresis of urine. The finding of light chains is sometimes more outstanding than the presence of monoclonal immunoglobulin. In few cases prevail the malignant clonal plasma cell proliferation without an important paraprotein production.

Under physiological circumstances fewer than 5 per cent of plasma cells are present in bone marrow. In myeloma multiplex their count increases to more than 10 to 20 per cent in bone marrow. Some plasma cells are bizzarly shaped. Cells containing two or more nuclei use to be present.

The clinical manifestation are due to the consequences of monoclonal protein (paraprotein) presence and to immunodeficiency. **In the bone marrow an invasion of malignant cells is found.** Migratory bone pain is frequently present with possibly occu-

ring spontaneous fractures. A severe complication is the hypercalcaemia and the syndrome of hyperviscosity. Fatigue, weakness, body weight loss and haemorrhagic diathesis, fever occur. In patients with severe damage of kidneys massive proteinuria or nephrotic syndrome may develop. The severity of the condition is evaluated by quantitative determination of monoclonal protein in serum and in urine. Chemotherapy is usually successful at the beginning of disease. It causes however a dangerous cytopenia with all consequences.

### 2.7.5.2 Waldenstrom's macroglobulinaemia

**This malignant disease is characterized by neoplasia arising from B-lymphocytes responsible for immunoglobulin M synthesis.** This condition has a course of long duration and occurs in older people. In patients arise usually anaemia with further symptoms – **lymphadenopathy hepatosplenomegaly, haemorrhagic diathesis and the blood hyperviscosity** of blood due to monoclonal IgM – a large molecule remaining in intravascular space. As consequence of high viscosity appears epistaxis retinal haemorrhages, mental confusion and congestive heart failure. Some IgM molecules praecipitate under lower temperature. This is why the syndrome of cryoglobulinaemia may become clinically manifest. Striking by cyanotic are acral parts exposed to cold, as fingers, nose, ears. On legs appear ulcerations and gangrenes due to vessel occlusion. Some IgM molecules act directly as antibodies against the erythrocytes. In these cases occur Raynaud's fenomenon with haemolytic anaemia.

In some patients the antimyelin activity of monoclonal IgM has been observed. This activity is considered to be the underlying cause development of peripheral neuropathy. Macroglobulin inhibits the thrombocyte aggregability contributing to the appearance of haemorrhagic diathesis.

In patients with Waldenstrom's macroglobulinaemia is sometimes the heavy chain disease identified (diagnosed). Malignant alteration of plasmocytes secreting a defective heavy chain with normal part Fc but with deletion of Fd parts, is involved.