Amongst various types of anaemia the most common are alimentary anaemia, haemolytic anaemia and anaemias due to haematological malignancies. However, not everyone realises that most of anaemias diagnosed in adults result from non-haematological conditions. This article will explain the pathogenesis and clinical picture of the most important secondary anaemias.

Anaemia: a common symptom of non-haematological conditions

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I. Anaemia of chronic disease

Anaemia of chronic disease (ACD) occurs in chronic inflammatory conditions, infections and cancers resulting from stimulation of the immune system. This type of anaemia is quite common. Apart from a chronic disease the definition of ACD also covers decreased concentration of serum ferritin and iron supplies in macrophages. Therefore other conditions, including chronic ones – where anaemia results from displacement of erythropoiesis from bone marrow by a malignant clone (e.g. leukemic), blood loss, haemolysis, endocrine disorders and chronic renal failure – are not considered to be ACD. However, ACD occurs in chronic bacterial infections (e.g. pneumonia, tuberculosis, lung abscess, urinary tract infections, meningitis, pelvic inflammatory diseases), viral infections (e.g. HIV), fungal infections, non-infectious chronic inflammatory conditions (e.g. systemic lupus, rheumatoid arthritis, vasculitis, sarcoidosis, inflammatory intestinal diseases), malignant conditions (solid tumours, Hodgkin's lymphoma and other non-Hodgkin's lymphomas, multiple myeloma). Sometimes the reason behind development of ACD remains unknown.

Pathogenesis of ACD is complex. Inflammatory/cancerous focuses cause activation of T4 lymphocytes and monocytes which release increased amounts of interleukins 1 and 10 as well as cytokines, including tumour necrosis factors TNFα and INFγ, which have an impact on macrophage cells, stimulating them to produce interleukin 6. These substances inhibit synthesis of erythropoiesis (EPO) and increase apoptosis of erythroblasts. Activation of macrophages by proinflammatory cytokines (TNFα) results in excessive erythrophagocytosis, which reduces the erythrocyte lifespan. Under the influence of cytokines the liver releases hepcidin which inhibits iron absorption from the duodenum. INFγ, lipopolysacharide (LPS) together with hepcidin decrease the expression of ferroportin (FPI) that enables release of iron from macrophage cytoplasm, which leads to retention of iron in macrophage cytoplasm, lack of iron availability for erythroblasts and decrease of its serum levels. All these mechanisms ultimately lead to a decrease in numbers of erythrocytes produced.

The clinical picture of these anaemias is diverse. Often the underlying disease is prevalent, however it often happens that the anaemia is the first symptom of a chronic disease to be diagnosed. Anaemia usually develops within 1–2 months from onset of a chronic disease and it does not progress. Haemoglobin concentration is usually around 9–11 g/dl, but in about 1% anaemia is severe. There is a general relationship between severity of the primary disease and severity of anaemia. It is worth mentioning that in case of malignancies anaemia appears also when bone marrow is not affected by expansion.

> Anaemia of chronic diseases is concurrent with chronic inflammatory diseases, infections and cancers

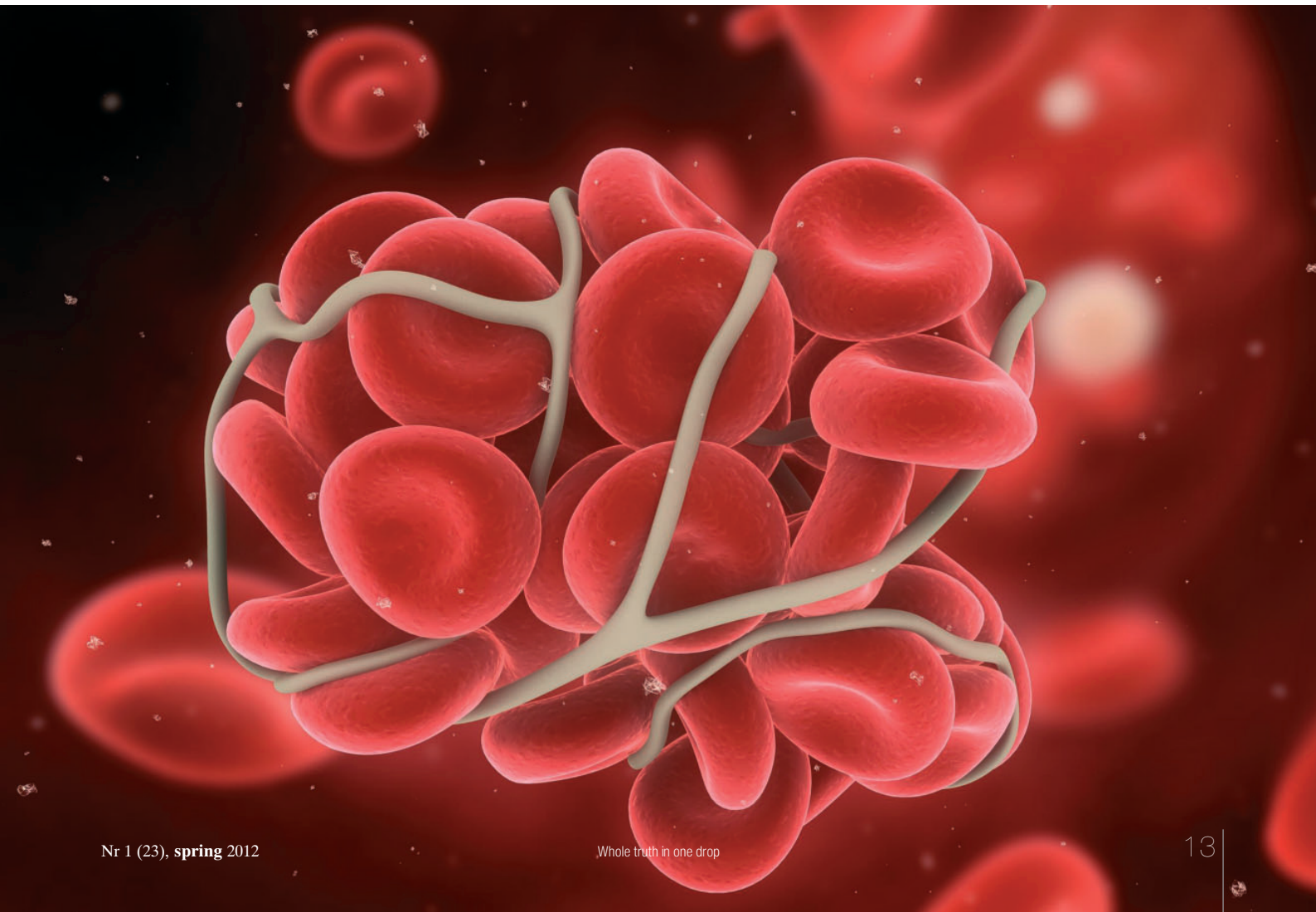
Typically, anaemia is normocytic and normochromic, however in more advanced

stages microcytosis and hypochromia can be prevalent. Hypochromia is more emphasized than microcytosis, and therefore it is possible that blood cells are hypochromatic, but their volume is still within normal range. Acceleration of microcytosis in ACD is slower than with iron deficiency. The number of reticulocytes is normal or decreased. Contrary to iron deficiency anaemia, blood smear often shows erythrocyte rolling. Serum iron and transferrin is decreased, but ferritin is within the normal range or is increased. Soluble transferrin receptor test, which should be normal or decreased, is a valuable differentiation tool between ACD with iron deficiency anaemia. Amongst other blood test, ESR is increased, fibrinogen, CRP, orosomucoid, ceruloplasmin, haptoglobin, amyloid A and C3 protein levels are increased. However, albumin levels are decreased. Panoptic myeloid staining does not provide diagnostic information and is therefore not recommended in ACD diagnosis. Bone marrow may show certain irregularities (e.g. decreased haemoglobinisation, unspecific increase of plasmocyte, macrophage or mastocyte numbers), but these are not pathognomonic symptoms of ACD. Thus, if the biopsy is carried out due to diagnostic difficulties, it is usually so that Perl's staining on free iron allows objective assessment of iron supplies in myeloid macrophages, unambiguously confirming or excluding (co) existence of iron deficiency. Typical changes in ACD are: increased amounts of iron in myeloid macrophages and decreased number (or lack of) sideroblasts.

Since ACD is only a „symptom" of another disease and not a disease itself, recession of anaemia is possible after recession of decreased activity of the underlying chronic condition. Thus all efforts shall be made to focus on an appropriate causal treatment, which is not always possible. Correct differentiation of ACD and iron deficiency anaemia is crucial for implementation of appropriate treatment. Finding iron deficiency would indicate the need for supplementation but in non-deficient ACD supplementation is not only ineffective but also contraindicated. In such situations, if it is not possible to cure the primary disease, the use of erythropoiesis stimulating agents (ESA) and/or transfusion of erythrocyte concentrate should be considered. It should be mentioned that in the majority of patients with ACD anaemia is slight to moderate and transfusions are not necessary.

II. Chronic renal anaemia

Chronic renal disease is a clinical condition which is often accompanied by anaemia. It is diagnosed when haemoglobin concentration is < 11.5 g/dl in women and <13.5 g/dl in men (<12.0 g/dl for those over 70 years old) and other possible reasons for anaemia have been excluded. It depends on the clinical stage of the disease, expressed by glomerular filtration rate (GFR). Clinically significant decrease of haemoglobin concentration usually occurs when GFR is falls below 30 ml/min/1.73m^2. Pathomechanics of anaemia in chronic renal disease is complex. The most important etiological factor of anaemia is insufficient production of erythropoietin (EPO). GFR does not correlate well with blood EPO concentration in all patients. For example, with renal damage in hypertension or in polycystic kidney disease, GFR values can be very low, but EPO can remain on relatively normal levels. In some patients witch chronic renal disease, EPO concentration can even increase. However, it must be remembered that even though EPO concentration is increased, it is still inadequately low in relation to the degree of anaemia. Apart from decrease of EPO the following factors can have an important role in pathogenesis of



anaemia in chronic renal disease, deficiency of substances necessary for blood cell production (iron, vitamin B_{12} and folic acid), suppression of erythropoiesis and shorter lifespan of erythrocytes.

Patients with chronic renal diseases often suffer from chronic blood loss, mainly due to gastrointestinal bleeding tendency, and – less often – due to hematuria. One must also take into account frequent blood collection for tests and haemodialysis, when some blood is always left in the haemodialysis tubing. The procedure itself also causes mechanical damage to erythrocytes, which is combined with adverse influence of uremic toxins. Iron deficiency in chronic renal disease can be of functional nature (mechanisms described above in ACD can be activated) or of absolute nature (decrease of supplies of iron due to chronic blood loss). Both these conditions are often connected.

> A thorough diagnostic process is necessary in each case of anaemia. Sometimes the conclusions can be surprising

With GFR < 30 ml/min/1,73 m^2 serum creatinine concentration correlates quite well with haemoglobin levels. However, it must be taken into account that possible water balance disorders which are typical in chronic renal disease may disguise or excessively emphasize the existing anaemia (in dehydration or overhydration respectively). In chronic renal disease anaemia is normochromic and normocytic. Most of erythrocytes assessed in blood smear are of normal shape, but often a population of echinocytes and sometimes also schistocytes, can be seen. The number of reticulocytes is in the normal range in most patients, but it can be increased or decreased, depending on the prevailing type of anaemia. The number of leukocytes and platelets is usually normal, but platelet function is often impaired by the influence of uremic toxins. Bone marrow is unspecific, general cellularity is normal and specific cell lines of haematopoiesis, especially erythropoiesis, have a normal morphology. Anaemia in chronic renal disease requires appropriate treatment, as it enhances overgrowth of the left ventricle and further, heart failure. Iron supplies must be corrected first, which in some patients may turn out to be sufficient to cure the anaemia. Appropriate supplementation is especially important in patients receiving ESA (erythropoietin) treatment. Lack of effectiveness of ESA treatment can be due to insufficient iron supply. Therefore it is important to maintain the ferritin levels at 200–400 $\mu g/l$ in patients treated with BSA.

III. Anaemia in liver diseases

Anaemia may appear in various chronic live diseases such as alcoholic cirrhosis, biliary cirrhosis, hemochromatosis or acute hepatitis. Decrease of blood haemoglobin levels in liver diseases is affected by an evident tendency to overhydration. Lifespan of erythrocytes shortens, due to hypersplenism which is concurrent with spleen enlargement, impaired erythrocyte metabolism and lipid irregularities in blood cell membrane). An important risk factor for anaemia in cirrhosis patients is increased frequency of bleeding (due to collateral circulation and plasma coagulation irregularities due to liver failure). Excessive alcohol consumption can cause sideroblastic anaemia, often with concurrent folic acid deficiency. Alcohol can also directly inhibit the erythropoiesis.

Anaemia in liver diseases is usually moderate, hardly dropping below 10 g/dl, unless there is bleeding or haemolysis present. In the majority of patients the mean corpuscular volume of erythrocytes is increased but it hardly exceeds 115 fl. There is no evident megaloblastosis in bone marrow (unless there is concurrent folic acid deficiency). Liver failure is often connected with the presence of acanthocytes, codocytes and possibly stomatocytes. Moderate thrombocytopenia can be observed in almost 50% of the patients with liver cirrhosis.

IV. Endocrine disorders

1. Hypothyroidism

It is quite a common reason of macrocytic – or possibly normocytic – anaemia. The anaemia is due to inhibited production of erythrocytes by the bone marrow. Decreased supply of thyroid hormones decreases oxygen use in the body and inhibits erythropoiesis synthesis. Macrocytosis can occur even with no anaemia present. Acanthocytes can be seen in blood smear of approximately 20% of the patients. There are no irregularities in the number of leukocytes or platelets. Substitution therapy with thyroxine cures the anaemia. However, it takes a few months and a marked increase in reticulocyte numbers – which is typical for various other types of deficiencies – is not observed. The gradual decrease of MCV is the indicator of anaemia subsiding.

2. Hypopituitarism

Normocytic, normochromic anaemia occurs in many cases of hypopituitarism. The number of produced erythrocytes is smaller in these patients. The influence of the pituitary gland on haematopoiesis is due to decreased stimulation by pituitary hormones, the end organs producing hormones which have a direct effect on haematopoiesis: the thyroid hormone, androgens and adrenocortical stem hormones. It must be emphasized that the growth hormone deficiency itself and prolactin deficiency can also be important here.

3. Hyperparathyroidism

Hypoparathyrodism (both primary and secondary, e.g. in chronic renal failure) can lead to normochromic and normocytic anaemia with normal or decreased level of reticulocytes. Myeloid testing in patients with primary hyperparathyroidism showed increased fibrosis and bone remodelling. These symptoms were accompanied by high level of calcium, alkaline phosphatase and parathormones in serum. The mechanism of anaemia development is not clear. Removal of parathyroid glands usually stabilises haemoglobin levels.

In everyday clinical practice, especially within basic outpatient care, it is usually assumed that iron supplementation, often with vitamin B_{12} and folic acid is the best course of treatment. Sometimes it brings the results, but in many patients it is ineffective or even harmful. A thorough diagnostic process is necessary in each case of anaemia. Sometimes the conclusions can be surprising. ■

References:
1. European Best Practice Guidelines on Anemia Treatment. Nephrol Dial Transplant 2004; 19 (Suppl. 2).
2. JS Caro i wsp.: Erythropoietin levels in uremic nephric and anephric patients. J. Lab Clin Med 1979; 93: 449.
3. J. Małyszko: Niedokrwistość w chorobach serca i nerek – spojrzenie nefrologa, Kardiologia Oparta na Faktach 2010; 1: 99–106.
4. J. P. Greer, J. Foerster, J. N. Lukens, G. M. Rodgers, F. Paraskevas, B. Glader (red): Wintrobe Clinical Haematology, Wydanie 11. Philadelphia, Lippincott Williams & Wilkins, 2006. 1451-1459.
5. A. Szczeklik, P. Gajewski: Choroby wewnętrzne.: Choroby wewnętrzne: stan wiedzy na rok 2011, Medycyna Praktyczna 2011; 1367.
6. B. J. Bain, D. M. Clark, B. Wilkins: Bone Marrow Pathology. Oxford, Blackwell Science 2010; 476–77.