Anaemias

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Goals

• outlining problems of anaemia recognition

• most frequent causes,
• diagnostic procedures
• treatment
# Anaemia definition (WHO)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small child (6 mo to 5 ys)</td>
<td>&lt;110 g/l</td>
</tr>
<tr>
<td>Child (5-12 ys)</td>
<td>&lt;115 g/l</td>
</tr>
<tr>
<td>Child (12-15 ys)</td>
<td>&lt;120 g/l</td>
</tr>
<tr>
<td>Adult woman (over 15 ys)</td>
<td>&lt;120 g/l</td>
</tr>
<tr>
<td>Pregnant woman</td>
<td>&lt;110 g/l</td>
</tr>
<tr>
<td>Adult male (over 15 ys)</td>
<td>&lt;130 g/l</td>
</tr>
<tr>
<td>Determination</td>
<td>Men</td>
</tr>
<tr>
<td>-----------------------------------</td>
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</tr>
<tr>
<td>Red cell count, x 10⁶ /μl (or x 10² /l)</td>
<td>5,1</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>15,3</td>
</tr>
<tr>
<td>Hematocrit, l/l x 100</td>
<td>45</td>
</tr>
<tr>
<td>MCV, fl</td>
<td>90</td>
</tr>
<tr>
<td>MCH, pg</td>
<td>30</td>
</tr>
<tr>
<td>MCHC, g/dl</td>
<td>33</td>
</tr>
<tr>
<td>Reticulocytes, %</td>
<td>10</td>
</tr>
<tr>
<td>Reticulocytes, x 10⁹ /l</td>
<td>50</td>
</tr>
<tr>
<td>Platelet count, x 10⁹ /l</td>
<td>245</td>
</tr>
</tbody>
</table>
Anaemia: symptoms

Extent of symptoms depends on...
- severity of anemia
- speed of its development: quick or slow
- presence of other diseases

Symptoms

- pallor of skin (hand creases) and mucous membranes (conjunctiva, oral mucosa)
- tiredness
- dyspnoe
- palpitation
- angina pectoris
- headache, pounding sensation in ears
Examination of the anaemic patient

• searching for signs of bleeding (at present or earlier)

• Signs of increased RBC destruction (hemolysis?)

• Bone marrow suppression?

• Iron deficiency? Why?

• Folic acid or B12 deficiency?
Examination of the anemic patient II

**Medical history**
- melaena?
- since what time?
- drug intake? (NSAIDs)
- geographic location?

**Physical examination**
- severity?
  - tachycardia, dyspnoea, fever, hypotension
  - hepatosplenomegaly, lymphadenopathy?
  - pallor: palm creases, mucous membranes
  - icterus?
  - petechiae? Infections?
Anaemias: Classification by kinetic approach

A. **Reduced RBC production**
   - BM stem cell disorder (AA)
   - bone marrow destruction (leukemia, metastasis of tumour, radiation, toxic)
   - deficiency anaemias (iron, B12, folic acid)

B. **Increased RBC destruction** (hemolízis: RBC lifespan < 100 days)
   - intrinsic” causes: disorders of RBC (congenit or acq.)
   - „extrinsic” causes: - pathologic substrances in plasma, antibodies,
     - vasculature, artificial heart valve

C. **Blood loss**
   - Acute
   - Chronic (Occult)

   apparent bleeding - hematemesis, melaena, metrorrhagia, epistaxis
   occult bleeding - slowly bleeding ulcer or carcinoma
Classification of anaemias II – morphological approach: According to RBC size and morphology

A. **Microcytic (MCV reduced)**
   - iron-deficiency anaemia
   - thalassaemias
   - some anaemias of chronic disease
   - Sideroblastic anaemia (MDS-SA)

B. **Normocytic (MCV normal)**
   - haemolytic anaemia
   - BM insufficiency
   - acute bleeding
   - anaemia of chronic diseases (ACD)
   - renal anaemia

C. **Macrocytic (MCV increased)**
   - B12-, folate deficiency
   - alcoholism
   - drugs
   - Reticulocytosis
   - myelodysplasia
Normal peripheral blood smear, thin, homogenous part
Evaluation of peripheral blood and bone marrow smears

Iron-deficiency anaemia, lack of prussian blue granules in the BM normoblasts

Megaloblastic anaemia, megaloblastic erythropoiesis in the bone marrow
Causes of microcytic anaemias

iron-deficiency: 50% of all anaemias!
  • especially common in children and women of child-bearing age

Thalassaemias

Other rare causes:
  • Some cases in anaemia of chronic disease (ACD)
  • Sideroblastic anaemia – seen in lead poisoning or a subtype of MDS
Iron homeostasis

Physiological iron need
- Women (before menopause) 2-3 mg/day
- Pregnancy 3-4 mg/day
- Males 1 mg/day
# Causes of iron deficiency

<table>
<thead>
<tr>
<th>Reproductive system</th>
<th>menorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI tract</td>
<td>oesophagitis, oesophageal varices, hiatus hernia, peptic ulcer, IBD, haemorrhoids carcinoma: stomach, colorectal</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>celiac disease, atrophic gastritis, gastrectomy</td>
</tr>
<tr>
<td>Dietary</td>
<td>vegans, elderly</td>
</tr>
<tr>
<td>Physiological</td>
<td>growth spurts, pregnancy</td>
</tr>
<tr>
<td>Others</td>
<td>PNH, frequent blood donation, hookworm</td>
</tr>
</tbody>
</table>
### Blood loss in gastrointestinal disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUTE</strong></td>
<td>Immediately following acute haemorrhage - RBC indices usually normal</td>
</tr>
<tr>
<td><strong>ACUTE ON CHRONIC</strong></td>
<td>RBC indices show low normal or marginally ↓, film shows mixture of normochromic &amp; hypochromic RBCs (dimorphic)</td>
</tr>
<tr>
<td><strong>CHRONIC</strong></td>
<td>RBC indices show established chronic Fe deficiency features ↓ MCV, MCH, platelets often ↑</td>
</tr>
</tbody>
</table>
Iron-deficiency anaemia: Medical history

- Rule out blood loss!
  - GI blood loss
  - Blood loss via menstruation
  - Haematuria
  - Blood loss during operation

- GI symptoms

- Diet: vegetarian diet, reduced iron absorption

- Drugs: NSAID, anticoagulants
Iron deficiency anaemia: physical examination

**Rare symptoms**
- Coilonychia
- Stomatitis angularis, cheilitis
- Glossitis

**Important symptoms**
- Teleangiectasia (Osler-disease)
- Abdominal mass
  - stomach, colon, uterus, kidneys
- Rectal mass/blood/melaena
Iron-deficiency: Diagnosis

**Serum ferritin:**
- corresponds with intracellular ferritin
- difficulty: elevated in infection, inflammation - always take in conjunction with CRP

**Serum iron, transferrin, TIBC:**
- practical problems
  - diurnal variation
  - negative acute phase marker

<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum iron</th>
<th>Transferrin</th>
<th>TIBC</th>
<th>Ferritin</th>
<th>sTFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>ACD</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑ or →</td>
<td>↓</td>
</tr>
</tbody>
</table>
## Laboratory tests in iron deficiency of increasing severity

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Fe deficiency without anemia</th>
<th>Fe deficiency with mild anemia</th>
<th>Severe Fe deficiency with severe anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow reticuloendothelial iron</td>
<td>2+ to 3+</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Saturation (Siron/TIBC), percent</td>
<td>20-50</td>
<td>30</td>
<td>&lt;15</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>Normal</td>
<td>Normal</td>
<td>9 to 12</td>
<td>6 to 7</td>
</tr>
<tr>
<td>Red cell morphology</td>
<td>Normal</td>
<td>Normal</td>
<td>Slight hypochromia</td>
<td>Hypochromia and mikrocyt</td>
</tr>
<tr>
<td>serum ferritin, ng/mL</td>
<td>20 to 200</td>
<td>&lt;20</td>
<td>&lt;15</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Other tissue changes</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Nail and epithelial changes</td>
</tr>
</tbody>
</table>
# Iron deficiency anaemia: Diagnostic workup

<table>
<thead>
<tr>
<th>Women of childbearing age</th>
<th>Menstrual blood loss highly probable. Serological exclusion of coeliacia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive serology</td>
</tr>
<tr>
<td></td>
<td>Family history</td>
</tr>
<tr>
<td>Males and older females</td>
<td>GI evaluation</td>
</tr>
</tbody>
</table>
Anulocytes, hypochromasias in iron-deficiency
Iron-deficiency anaemia:

Treatment

- **Iron-sulfate 3x200 mg per os**, effective in the majority of cases
  side effects: GI complaints (constipation, diarrhoea)

- Iron-deficiency anaemia refractory to iron: iv. iron treatment
  - continued blood loss
  - insufficient iron intake
    - non-compliance
    - insufficient dosage
    - malabsorption
  - incorrect diagnosis
Deficiency anemia caused by H. pylori

1. Colonisation of the gastric mucosa
   - Acute inflammation
   - Chronic active gastritis
   - Gastric atrophy and achlorhyrdia

2. Iron absorption ↓
   - Fe-deficiency
   - Fe-deficiency anaemia

3. Immune response
   - Against H. pylori
   - Against self
   - Mol. mimicry

4. Autoimmune destruction of the parietal cells (IF ↓)
   - B12 absorption ↓
     - Pernicious anaemia

5. MCV
   - microcytosis
   - macrocytosis
Anaemia of chronic disease (ACD)

- Increase in IL-1, IL-6, TNF-alfa levels:
  - inhibiting the effect of EPO
  - resulting in sequestration of iron in BM macrophages
- Increased RBC destruction
- Release of positive AFF peptide Hepcidin: decreased absorption
Differential diagnosis of iron deficiency anaemia (IDA) vs anaemia of chronic disease (ACD)

Determination of soluble transferrin receptor

Iron deficiency (IDA)  ACD: Anaemia of chronic disorders  Combined causes  Normal
Anemia of chronic disease (ACD) - bone marrow iron stain

Increased iron stores !!
Macrocytic anaemia

Macrocytic ≠ megaloblastic
- megaloblastic is used for the description of the bone marrow, when maturation of nucleus and cytoplasm are asynchronous

Macrocytic, not megaloblastic
- Alcohol
- Liver diseases
- Hemolysis + reticulocytosis
- Hypothyreosis
- Pregnancy
- Sphaerocytosis

Megaloblastic anaemia
- B12 or folic acid deficiency
- Myelodysplasia
- Drug-induced (azathioprine, hydroxycarbamide)
Causes and pathomechanism of macrocytosis

• **Disturbances of the DNA synthesis**
  - B 12 vitamin deficiency
  - Folic acid deficiency
  - Drugs: Litalir (hydroxycarbamide)
    Imuran (azathioprine)
    Methotrexate

• **Circulating immature RBCs**
  - Reticulocytosis
  - Anaemia aplastica
  - Pure RBC aplasia

• **Primary bone marrow disorders**
  - Myelodysplastic syndromes
  - Congenital diserythropoietic anaemia (CDA)

• **Lipid abnormalities**
  - Liver disease
  - Hypothyreoidism
  - Hyperlipidaemia

• **Unknown causes**
  - Alkohol abuse
  - Multiple myeloma
## Causes of cobalamin deficiency

<table>
<thead>
<tr>
<th>Dietary deficiency</th>
<th>vegans</th>
<th>Deficiency of absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERNICIOUS ANAEMIA</strong></td>
<td>Commonest, due to autoimmune gastric atrophy resulting in loss of intrinsic factor production required for absorption of $\text{B}_{12}$.</td>
<td><strong>PERNICIOUS ANAEMIA</strong></td>
</tr>
<tr>
<td>Following total gastrectomy</td>
<td>May develop after major partial gastrectomy.</td>
<td>Following total gastrectomy</td>
</tr>
<tr>
<td>Ileal disease</td>
<td>Resection of ileum, Crohn’s disease.</td>
<td>Ileal disease</td>
</tr>
<tr>
<td>Blind loop syndromes</td>
<td>E.g. diverticulae or localised inflammatory bowel changes allowing bacterial overgrowth which then competes for available $\text{B}_{12}$.</td>
<td>Blind loop syndromes</td>
</tr>
<tr>
<td>Malabsorptive disorders</td>
<td>Tropical sprue, coeliac disease.</td>
<td>Malabsorptive disorders</td>
</tr>
<tr>
<td><strong>Fish tapeworm</strong></td>
<td><em>Diphyllobothrium latum.</em></td>
<td><strong>Fish tapeworm</strong></td>
</tr>
<tr>
<td>Transcobalamin II deficiency</td>
<td>Deficiency of transporter protein</td>
<td>Transcobalamin II deficiency</td>
</tr>
</tbody>
</table>
Macrocytic aemia: Clinical symptoms

Typical patient with pernicious anaemia
Macrocytic anaemia

Clinical presentation

**Cobalamin deficiency:**
causes symptoms after several years

Might occur in young people as well, usually associated with other autoimmune disorders (vitiligo, alopecia, autoimmune poliglandular insuff type 2: + Hashimoto thyreoiditis, Addison-disease)

**Folic acid deficiency:**
manifestation after 4-5 months
Macrocytic anaemia

Laboratory examinations

Reticulocyte count

Examination of the peripheral blood film

Liver function tests

TSH determination

B12, folic acid levels

Bone marrow examination, cytogenetics
Macrocytic anaemia

Laboratory findings

- LDH ↑↑
- Bilirubin ↑ (not conjugated)
- Haptoglobin ↓
- Fe ↑

Slight hemolysis

Reticulocyte ↓

Ineffektive haemopoiesis
Macrocytic anaemia
Laboratory examinations

- **Se B12 determination**
  - >300 pg/ml normal
  - 200-300 pg/ml borderline cases, cobalamin deficiency might occur
  - <200 pg/ml decreased level, cobalamin deficiency

- (Se folic acid determination)
  - > 4 ng/ml: no folic acid deficiency
  - < 2 ng/ml: folic acid deficiency
Macrocytic anaemia

Laboratory examinations

Serum B12 levels ↓

↓

if no antibodies to IF present

↓

(Schilling test)
B12 deficiency anaemia

Lab exams: Schilling test
B12 deficiency anaemia
Clinical symptoms

Elusive neurological symptoms might be the earliest or only finding!!!

- Symmetric, mainly lower extremity neuropathy,
  - paresthesia, ataxia, weakness, spasticity
  - Patom: degeneration of the posterior and lateral spinal fasciculi

Disturbances of memory, demencia, irritability, personality changes
  Patom: CNS and peripheral nervous system axon degeneration
B12 deficiency anaemia
Clinical symptoms

Impairment of cells with quick metabolism:

- Glossitis
- Malabsorption
- Vaginal atrophy
- Frequent cystitis
Neurological symptoms caused by cobalamin deficiency

- 24% of patients had no anaemia
- 19% of patients had no macrocytosis
- 14% of pts had neither

- Key diagnostic finding: hypersegmentation of neutrophils in the peripheral blood smear
B12 deficiency anaemia
Full blood count

- Macrocytic anaemia
- Leucopenia
- Thrombocytopenia
- Peripheral smear:
  - Ovalo-macrocytosis
  - Hypersegmented neutrophils
  - Segmented eosinophils (pseudo Pelger-Huet anomaly)
B12 deficiency anaemia
Bone marrow findings

• Highly hypercellular

• Megaloblastic erythroid hyperplasia
  – Mauration asynchrony of the nucleus and the cytoplasm
  – Nuclear anomalies: karyorrhexis, two nuclei stb

• Huge metamyelocytes, bands
Megaloblastic erythropoiesis in the bone marrow
## Causes of folic acid deficiency

| ↓ intake | Poor nutrition (poverty), old age. |
| ↑ requirements/losses | Pregnancy, ↑ cell turnover, e.g. haemolysis, exfoliative dermatitis, renal dialysis. |
| **Malabsorption** | Coeliac disease, tropical sprue, Crohn’s and other malabsorptive states. |
| **Drugs (induce folate malabsorption)** | Phenytoin, barbiturates, valproate, oral contraceptives, nitrofurantoin. |
| **Antifolate drugs** | Methotrexate, trimethoprim, pentamidine. |
| **Alcohol** | Poor nutrition plus a direct depressant effect on folate levels which can precipitate clinical folate deficiency. |
Megaloblastic anaemia

Treatment

**B12 VITAMIN:** 1 mg im. for 5 days
later 1 mg im. EVERY 1-3 MONTHS, LIFELONG !!

**FOLIC ACID:** 5 mg /per os

If *transfusion* is necessary, *increased care* because of cardiomyopathy caused by B12 deficiency!
Hemolytic anaemias
## Common causes of hemolytic anemia in the adult

### Extravascular destruction of red blood cells

#### Intrinsic red blood cell defects
- Enzyme deficiencies (e.g., G6PD or pyruvate kinase deficiencies)
- Hemoglobinopathies (e.g., sickle cell disease, thalassemias, unstable hemoglobins)
- Membrane defects (e.g., hereditary spherocytosis, elliptocytosis)

#### Extrinsic red blood cell defects
- Liver disease
- Hypersplenism
- Infections (e.g., bartonella, babesia, malaria)
- Oxidant agents (e.g., dapsone, nitrites, aniline dyes)
- Other agents (e.g., lead, snake and spider bites)
- Large granular lymphocyte leukemia
- **Autoimmune hemolytic anemia (warm- or cold-reacting, drugs)**
- Intravenous immune globulin infusion

### Intravascular destruction of red blood cells

- Microangiopathy (e.g., aortic stenosis, prosthetic valve leak)
- Transfusion reactions (e.g., ABO incompatibility)
- Infection (e.g., doxtridial sepsis, severe malaria)
- Paroxysmal cold hemoglobinuria
- Paroxysmal nocturnal hemoglobinuria
- Following intravenous infusion of Rho(D) immune globulin
- Following intravenous infusion with hypotonic solutions
- Snake bites
<table>
<thead>
<tr>
<th>Causes of transfusion-associated hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-Mediated</td>
</tr>
<tr>
<td>Acute hemolytic transfusion reaction</td>
</tr>
<tr>
<td>Delayed hemolytic transfusion reaction</td>
</tr>
<tr>
<td>Nonimmune-Mediated</td>
</tr>
<tr>
<td>Thermal Injury</td>
</tr>
<tr>
<td>Heat</td>
</tr>
<tr>
<td>Cold</td>
</tr>
<tr>
<td>Osmotic injury</td>
</tr>
<tr>
<td>Mechanical injury</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Congenital hemolytic anemia</td>
</tr>
<tr>
<td>Acquired hemolytic anemia</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
</tbody>
</table>
Recognizing hemolysis

- **new onset** of pallor and anemia
- **jaundice** with increased unconjugated bilirubin
- gallstones
- splenomegaly
- presence of circulating **spherocytic** RBSs
- **increased serum lactate dehydrogenase** (LDH)
- **reduced** (or absent) level of serum **haptoglobin**

- a **positive direct antiglobulin** test (Coombs test)

- **increased reticulocyte percentage** or absolute reticulocyte number, indicating the bone marrow's response to the anemia
Confirming hemolysis

The combination of an increased serum LDH and a reduced haptoglobin is 90 percent specific for the presence of hemolysis.

while the combination of normal serum LDH and a serum haptoglobin >25 mg/dL is 92 percent sensitive for ruling out hemolysis.
Peripheral blood smear abnormalities suggesting extravascular hemolysis:

- spherocytes,
- microspherocytosis,
- elliptocytes, "bite" or blister cells,
- acanthocytes,
- teardrop red cells.

Abnormalities that suggest that the hemolysis is intravascular

- presence of free hemoglobin in plasma or urine
- a urine sediment positive for iron (hemosiderinuria)
- in rare cases, the presence of circulating red cell "ghosts."
High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.
a microangiopathic hemolytic anemia (MAHA) with marked red cell fragmentation.
spherocytes
microspherocytes and elliptocytes
Autoimmune hemolytic anaemia (AIHA)

Treatment

First line:
- methylprednisolone 1 mg/kg/day

2nd Line:
- rituximab (anti-CD20 monoclonal antibody)
- Splenectomy

3rd line:
- Cyclophosphamide (Endoxan)
- Azathioprine (Immuran)
- Cyclosporine A (Sandimmun)

Acute life-threatening AIHA:
- Red cell transfusion - controversial
ANAEMIA CAUSED BY BONE MARROW DISORDERS

Hypoproliferativa anaemias - low reticulocyte count

Aplastic anaemia

Malignant haematological disorders
  - Leukemias
  - Lymphomas
  - Multiple myeloma
  - Myelodysplasia
  - Myelofibrosis

Bone marrow metastasis of solid tumors
Aplastic Anaemia (AA)

Definition:
Pancytopenia as a result of hypocellular bone marrow. Distinct from iatrogenic hypocellularity, eg. Aplasia following chemotherapy.

Epidemiology:
Incidence is about 0.2/100K/year.
Frequently involved age groups are adolescents and older adults.

Pathogenesis:
- Effect of immunosuppressive therapy suggests autoimmune mechanism.
- Rarity and twin studies suggest genetic predisposition.
## Classification of Aplastic Anemia

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Inherited</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDIOPATHIC</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SECONDARY</strong></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>Fanconi's anemia</td>
</tr>
<tr>
<td>Drugs and chemicals</td>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td>Regular effects</td>
<td>Shwachman-Diamond syndrome</td>
</tr>
<tr>
<td>Idiosyncratic reactions</td>
<td>Reticular dysgenesis</td>
</tr>
<tr>
<td>Idiosyncratic reactions</td>
<td>Amegakaryocytic thrombocytopenia</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus (infectious mononucleosis)</td>
<td>Preleukemia (monosomy 7, etc.)</td>
</tr>
<tr>
<td>Hepatitis (non-A, non-B, non-C hepatitis)</td>
<td>Nonhematologic syndrome (Down, Dubowitz, Seckel)</td>
</tr>
<tr>
<td>Parvovirus B19 (transient aplastic crisis, PRCA)</td>
<td></td>
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<tr>
<td>HIV-1 (AIDS)</td>
<td></td>
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<tr>
<td><strong>Immune diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic fasciitis</td>
<td></td>
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<tr>
<td>Hyperimmunoglobulinemia</td>
<td></td>
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<tr>
<td>Thymoma/thymic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Graft-versus-host disease in immunodeficiency</td>
<td></td>
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<tr>
<td><strong>Paroxysmal nocturnal hemoglobinuria</strong></td>
<td></td>
</tr>
<tr>
<td>Subclinical T-cell clones of large granular lymphocyte leukemia (up to 7% of AA)</td>
<td></td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Classification of single cytopenias</td>
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<tr>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td><strong>Pure red cell aplasia (PRCA)</strong></td>
<td>Congenital PRCA (Diamond-Blackfan anemia)</td>
</tr>
<tr>
<td><strong>Neutropenia/agranulocytosis</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Kostmann's syndrome</td>
</tr>
<tr>
<td>Drugs, toxins</td>
<td>Shwachman-Diamond syndrome</td>
</tr>
<tr>
<td><strong>Pure white cell aplasia</strong></td>
<td>Reticular dysgenesis</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
</tr>
<tr>
<td>Drugs, toxins</td>
<td>Amegakaryocytic thrombocytopenia</td>
</tr>
<tr>
<td>Idiopathic amegakaryocytic</td>
<td>Thrombocytopenia with absent radii</td>
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Aplastic anaemia
Approach to the patient

**Medical history:**
- symptoms of anaemia, thrombopenia and leukopenia
- onset may be sudden or gradual
- prevalence of previous drug use, chemical exposure or viral infections should be explored

**Physical examination:**
- signs of **bleeding**, petechiae, prolonged menstrual flow
- pallor and symptoms of **anaemia**
- **infections** – not common at presentation

**NOT** characteristic: lymphadenomegaly, splenomegaly
Aplastic anaemia
Diagnostic studies

Peripheral blood studies:
• Large erythrocytes, paucity of platelets and granulocytes
• Decreased number of reticulocytes and occasionally lymphocytes
• May start with the involvement of 1-2 cell lines → later progression to pancytopenia
• NOT characteristic:
  • Immature myeloid forms: consider CML, AML, MDS
  • Nucleated erythroid forms, dacryocytes: myelofibrosis, invasion by tumor

Bone marrow studies:
• Aspirate:
  • Mainly red cells, lymphocytes and stromal cells
  • NOT characteristic: „dry tap” – look for fibrosis or myelophthisis
• Trephine biopsy: preferred diagnostic method
  • Increased proportion of fat tissue, hemopoietic tissue <25%
  • Dysplastic changes, chromosomal abnormalities suggest MDS
Aplastic anaemia
Treatment options

Allogenic haematopoetic stem cell transplant (allo-HSCT):
- In younger patients
- Allo-HSCT from matched sibling donors: 90% long-term survival rates in children
- High resolution HLA matching and improved conditioning and GVHD prevention regimens → better results with MUD HSCT as well
- More modest results as age increases

Immunosuppressive therapy:
- In elderly patients
- Combination of anti-thymocyte/anti-lymphocyte globulin (ATG/ALG) and cyclosporin A
- Induces remission in 60-65% of patients, but significant risk of relapse
- Other agents: high dose cyclophosphamide, androgenic hormones

Supportive care:
- Anaemia: red cell transfusions on demand
- Thrombopenia: platelet transfusion on demand
- Neutropenia: aggressive approach with antibiotics, consider G-CSF
Myelodysplastic syndrome
Refractory anaemia with ring Sideroblasts (RARS)
Summary
Essentials of anaemia management

- Diagnostic steps before the beginning treatment!
- First step is to look at MCV and reticulocyte count
- Anaemia is the symptom and not the disease itself!!!
- Bone marrow disorders are among the rare causes of anaemias
- IDA and anaemia of chronic disease (ACD) are the most frequent
- Importance of peripheral smear in the evaluation of anaemias
- Anaemia is often caused by multiple causes
PNH – 30 years of observation

Judit Demeter

First Department of Medicine
Semmelweis University
Patient K. Zs., male, born 1961

- **Initial symptoms:**
  - Epigastric and umbilical pain biweekly!
  - In these periods darker urine
  - Malaise
  - Nausea and vomiting
  - Subicterus-jaundice
  - Hepato-splenomegaly
  - Anemia (partly hemolytic, partly iron-deficient)
    - Hb: 80 g/L
    - WBC: 9.4 G/L
    - Platelet count: 150 G/L
    - Reticulocyte: 45 %
    - Serum bilirubin: 29.3 μmol/L, conjugated: 9.8 μmol/L
    - LDH: 987 IU/L
Hemolytic crisis (1981)

- Intense epigastric pain
- Ascites
- **Laboratory findings:**
  - DAT: negative
  - Normal serum folic acid, B12 levels
  - Serum ferritin: 10 ng/ml
  - **GAPA: 4%, 11 score**
  - **Bone marrow cytology:** Hyperplastic, ineffective erythropoesis, slightly reduced granulopoesis, no other pathologic findings. Prussian blue: no stainable iron (extracell:0, no sideroblasts)
  - **Splenopancreatography:** vena portae thrombosis
  - **Liver biopsy:** centrilobular liver necrosis, veno-occlusive disease?
  - July 1981: exploratory laparotomy (thrombosis venae portae, thromb art. mesent.) + splenectomy
  - Ascites ceased
Hemolytic crisis, ascites, pleural fluid (1982)

Pleural fluid (transudate): accumulation due to thrombosis of the right axillary and subclavian veins

Red blood cell half-life (1981): 15.6 days (severely decreased)
RBC osmotic resistance: normal

Treatment:
– Regular blood transfusions
– Acenocoumarol anticoagulation
– Oral iron and folic acid
– Diuretic therapy because of the ascites
Diagnosis of PNH (1985)

• Admission because of:
  – Abdominal spasms
  – weakness
  – Recurrent fever, infections

Hemolytic attack

Laboratory findings:
- Hemoglobin: 90 g/L
- Reticulocytes: 9.7%
- Platelet count: 220 G/L
- WBC: 9.2 G/L
- Serum bilirubin: 115 µmol/L; conjugated: 57 µmol/L
- LDH: 1250 IU/L
- Hemosiderinuria
- Hb-electrophoresis: normal
- Porphyria-test: negative
Diagnosis of PNH (1985)

• **Final steps of the diagnosis:**
  – Sucrose (sugar-water) test: positive
  – HAM (acidified serum test): positive

• **Treatment:**
  – Treatment of acute crisis with prednisolone, discontinued later
  – Continuation of oral anticoagulation (acenocoumarol)
Laboratory values over the course of the disease

- **Time of diagnosis**
- **Splenectomy**

- **Graph elements**:
  - **Hemoglobin (g/L)**
  - **Platelet count (G/L)**
  - **Reticulocyte count (G/L)**

- **Axes**:
  - **Time elapsed since start of observation (months)**
  - **Y-axis values** range from 0 to 600
Follow up

• Repeated hemolytic crises

• Surgery because of mechanical ileus caused by peritoneal adhesions (in 1988 and 1996)

• Cirrhosis of the liver on the basis the former vascular lesions. Recurrent ascites, necessitating diuretic therapy

• Folic acid replacement and oral iron therapy since 1997, with little effect

• Vitamin D replacement, with little effect
• Tests for congenital causes of thrombophilia: negative

• RBC transfusions minimised
Recent findings (Autumn 2011)

- Laboratory values (2011.09.28.):
  - Hb: 74 g/L
  - WBC: 5.7 G/L
  - Platelet count: 95 G/L
  - Reticulocyte count: 6.4%
  - Reticulocyte index : 2.06
  - LDH: 4350 IU/L
  - Total bilirubin: 55.4 µmol/L direct: 15.6 µmol/L
  - ALP: 478 IU/L (80-300)
  - ASAT: 149 IU/L (1-46)
  - Ferritin: 10 ng/mL (20-200)
  - Creatinine: 53 µmol/L (normal range)
  - GFR: normal
  - BNP: 123 pg/mL (0-100)
PNH has been diagnosed in our patient in 1985. The symptoms are known to exist since 1975.

Significant impact on survival

Since 1986 not any more

Significant impact on mortality

- - + + -
1. PNH clone detected – **yes** or no

2. PNH-clone size in WBC (**60.9% in granulocytes and 61.5% in monocytes**)  

3. PNH-clone size in RBC with distribution of Type I (**90.6%**), Type II (**5.3%**) and Type III cells (**34.1%**)

4. Flow cytometry **graph** of PNH clone is provided

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P. A. 38 years old female patient

History of complaint

• Severe anaemic episode the age of 9 months
  – Presentation following fever
  – Received red cell transfusions at that age

• Further anaemic shubs requiring transfusion, following infections:
  – At 18 months
  – At 30 months
  – At 31 months
  – Repeatedly at the age of 3 years

• Splenectomy at the age of 3.5ys, no transfusion need for the next two years.
P. A. 38 years old female patient

History of complaint II.

- Repeated transfusions following infections
- At the age of 7: mild direct and indirect antiglobulin test positivity
  → Corticosteroid therapy without significant results – transfusion required after infection while tapering steroids
- No transfusion after the age of 13 years
- No written documentation of attempts to rule out existence of accessory spleen
- Cholecystectomy in 2008 – gall stones are a hallmark of hemolysis
P. A. 38 years old female patient
Current presentation

- Admission in September 2013 because of severe anaemia following pneumonia
- Laboratory findings:
  - Hb: 51 g/L
  - MCV: 120 fL
  - Platelet count: 1228 G/L
  - Reticulocyte: 606‰
  - Total bilirubin: 57.6 μmol/L
  - Ferritin: 1631 μg/L
  - Negative DAT and no anti-RBC antibodies
  - Polychromatophilic RBCs, anisocytosis, poikilocytosis, basophilic stippling and several stomatocytes
P. A. 38 years old female patient

Current presentation

- **CXR**: pneumonia involving left lung
  - Combined antibiotic treatment
  - Signs of infection regressed

- **4 Units of red cell transfusion**

- **Follow-up findings after 6 days**:
  - Hb: 102 g/L
  - MCV: 105 fL
  - Reticulocyte count: 408‰
  - Platelet count: 1083 G/L
  - Hb electrophoresis: no anomaly detected
Thank you for your attention!