Evaluation of chronic pancytopenia

from clinics to decision making

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What is the problem?

- Abnormal reduction in all three cell lines
- Chronic disorder
  - More than 6 months (no recommended definition)
  - Excludes transient causes of pancytopenia
- Particular situations of pancytopenia
  - Decreased platelets, WBC and hemoglobin, even if RBC are normal
  - Decreased platelets, hemoglobin and neutrophils, even when lymphocytes are increased (CLL; lymphoma)
- Diagnostic approach – distinction between
  - Congenital cytopenia
  - Non malignant cytopenia (reactive)
  - Cytopenia related with malignant disorders
Type of pathological abnormalities affecting the blood cell system

Disorders of production or release from the marrow

Disorders of disposal or utilization

Disorders of or in the circulation

- Decreased production
- Ineffective hematopoiesis
- Pooling of cells (spleen)
- Margination of neutrophils
- Peripheral destruction
- Hypersplenism
Disorders of the production or release from the marrow

**Decreased production of the bone marrow**
- Marrow failure syndrome (aplastic anemia)
- Infiltration by lymphoma, myeloma, cancer
- Fibrosis
- Acute leukemia

**Ineffective hematopoiesis ➔ destruction of blood cells in the marrow**
- Megaloblastic anemia (periciosa)
- Myelodysplastic syndrome (PNH)
Disorders of disposal or utilization

- Immucytopenia
  - Evens syndrome
- Sequestration in the spleen
  - Most often associated with chronic liver disease, cirrhosis, chronic alcoholism
- Hemopathocytosis
  - Infection
  - Tumor
- Paroxysmal nocturnal hemoglobinuria (PNH)
  - Hemolysis
  - Marrow failure
- Disseminated intravascular coagulopathy (DIC)
- Pregnancy
Pancytopenia may have multiple, unrelated causes

- A combination of pathological processes may lead to pancytopenia
- Each of the cell lines is independently affected by a different process
- Consequences
  - requires further investigations for each individual cause
  - different treatment of the cell lines
Exercise case 1

Mr. JD; 55 yrs, male, Swiss
Patient is a railway worker, and consulted his doctor for tiredness, malaise, and anorexia.

He was found to be mildly jaundiced with an enlarged irregular hepatomegaly and considerable ascites.

Some blood tests were performed

Morphology:
Anisocytosis, macrocytosis, target cells, stomatocytes
What we know

- Chronic liver disease probable
- Pancytopenia could be the consequence of
  - Portal hypertension with hypersplenism
- Anemia multifactorial?
  - Bleeding
  - Hemolysis
  - hypersplenism

Open questions

- type and cause of the liver disease
  - Alcohol abuse?
  - Chronic viral hepatitis?
- Size of the spleen, portal flow rate
  - Is there a hypersplenism?
- Can we exclude an MDS?
  - Macrocytosis but no dysplasia of the neutrophils
  - Splenomegaly unusual in MDS
What we learn from this case

- History of the patient
  - Alcohol abuses
- Sonography revealed enlarged liver and spleen, as well as portal hypertension
- Ascitic fluid was a transudate
- Hepatitis virus studies negative for Hepatitis-A, -B and -C
- Ferritin 498 mg/L (references 30-250)
- To be on the safe side, marrow examination was performed:
  - Normocellular marrow with normal hematopoiesis
- Pancytopenia due to chronic liver disease with portal hypertension and hypersplenism
  - Macrocytosis due to liver disease
  - Anemia multifactorial
- Diagnosis mainly based on history of the patient, clinical examination and basic blood tests
- Bone marrow examination not absolutely necessary in the present case
  - Despite MDS could not be excluded without marrow examination
Mrs. ML; 46 yrs, female, Swiss
Patient presented at the hospital with marked weakness as well as a feeling of fullness in her upper abdomen

On the examination she was found to be very pale. The spleen was massively enlarged

Some blood tests were performed

Morphology:
Anisocytosis, poikilocytosis, tear drops, large plateles, megakaryocytic XXX

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>78</td>
<td>g/L</td>
<td>120-160</td>
</tr>
<tr>
<td>MCV</td>
<td>88</td>
<td>fL</td>
<td>80-95</td>
</tr>
<tr>
<td>Reti.</td>
<td>7</td>
<td>x10⁹/L</td>
<td>40-100</td>
</tr>
<tr>
<td>WBC</td>
<td>2.9</td>
<td>x10⁹/L</td>
<td>3.5-10.0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>0.98</td>
<td>x10⁹/L</td>
<td>2.0-7.0</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.26</td>
<td>x10⁹/L</td>
<td>0.2-0.8</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>1</td>
<td>%</td>
<td>0</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>1.5</td>
<td>%</td>
<td>0</td>
</tr>
<tr>
<td>Normoblasts</td>
<td>5</td>
<td>n/100 WBC</td>
<td>0</td>
</tr>
<tr>
<td>Platelets</td>
<td>695</td>
<td>x10⁹/L</td>
<td>150-450</td>
</tr>
</tbody>
</table>
What do we know and how to proceed

**What is the diagnosis of the peripheral blood changes?**

- Bicytopenia and thrombocytosis
- with leukoerythroblastic changes
- Megaloblastic anemia is improbable
  - Normal MCV, morphology (no hypersegmented neutrophils), no splenomegaly
- MDS is unlikely
  - No dysplastic changes in blood
  - Splenomegalie
  - But MDS cannot be definitively ruled out

**Provisory diagnosis**

- Myelofibrosis with splenomegaly
- Other pathology of both, the spleen and marrow

**Bone marrow investigation**

- Aspiration: dry tap
- Histology
  - Hypercellular marrow
  - Increased abnormal megakaryopoiesis
  - Fibrosis
- Genetic analysis
  - JAK2 positive (62%)
What we learn from this case

- Examination of the patient
  - Splenomegaly
- Peripheral blood gives a very important hint
  - Bicytopenia
  - Thrombocytosis
  - Tear drops
  - Leukoerythroblastic changes
- very suggestive for
  - Myeloproliferative disorder with myelofibrosis
- Bone marrow investigation and JAK2
  - Definitive diagnosis

Look carefully your patients and the blood counts/films
**Exercise case 3**

Mr. RA; 58 yrs, male, Swiss
Patient has a long history over 4 years, with symptoms of exhaustion, easy bruising and prolonged bleeding from injuries. He was followed by his family doctor and received from time to time a transfusion.

On the examination there was a pallor, few petechiae at his legs, but no other findings

Morphology peripheral blood:
Marked anisocytosis, and poikilocytosis, rare blasts

**Based on bone marrow examination, the diagnosis of aplastic anemia was retained**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>75</td>
<td>g/L</td>
<td>140-180</td>
</tr>
<tr>
<td>MCV</td>
<td>108</td>
<td>fL</td>
<td>80-95</td>
</tr>
<tr>
<td>Reti.</td>
<td>38</td>
<td>x10⁹/L</td>
<td>40-100</td>
</tr>
<tr>
<td>RDW</td>
<td>21</td>
<td>%</td>
<td>&lt;14</td>
</tr>
<tr>
<td>WBC</td>
<td>0.8</td>
<td>x10⁹/L</td>
<td>3.5-10.0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>0.24</td>
<td>x10⁹/L</td>
<td>2.0-7.0</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>0</td>
<td>%</td>
<td>0</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>0</td>
<td>%</td>
<td>0</td>
</tr>
<tr>
<td>Blasts</td>
<td>0.5</td>
<td>%</td>
<td>0</td>
</tr>
<tr>
<td>Normoblasts</td>
<td>0</td>
<td>n/100 WBC</td>
<td>0</td>
</tr>
<tr>
<td>Platelets</td>
<td>45</td>
<td>x10⁹/L</td>
<td>150-450</td>
</tr>
</tbody>
</table>
What is the diagnosis of the peripheral blood changes?

- Pancytopenia
- Pancytopenia with macrocytosis

The diagnosis of aplastic anemia is suspect

- RDW too high for aplastic anemia
- Marked anisocytosis and poikilocytosis is unusual
- No blasts in aplastic anemia (even not very rare blasts)

Provisory diagnosis

- Pancytopenia with macrocytosis and rare blasts
- With hypoplastic marrow

Differential diagnosis of hypoplastic marrow

- Aplastic anemia
- PNH/Aplastic anemia syndrome
- Hypoplastic MDS
- Hypoplastic leukemia
What we learn from this case

- Discrepant findings between peripheral blood and bone marrow
  - Rare Blasts in peripheral blood
  - Aplastic marrow
- Review of the bone marrow slides
  - No new findings
- Second bone marrow examination 3 months later
  - Nests of erythropoiesis with dysplasia
  - Few nests of megakaryopoiesis with micromegakaryocytes
  - Few blasts
  - Increase of CD34+ cells in immunohistochemistry

**Integrated diagnosis of all finding suspected another diagnosis.**

**Sometimes follow-up with repetitive marrow examination is necessary**
Systematic evaluation of pancytopenia: what the hematologist/hematopathologists needs

- Clinical findings
- Peripheral blood
- Additional blood tests
- Imaging (radiographic)
- Bone marrow examination
- Integrated diagnosis
- Follow-up (as part of the evaluation)
### History of the patient

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of the symptoms</td>
<td>MDS long; SAA short history</td>
</tr>
<tr>
<td>Family history</td>
<td>Congenital, hereditary disease</td>
</tr>
<tr>
<td>Age of the patients</td>
<td>MDS in adult, elderly patients; SAA at any age</td>
</tr>
<tr>
<td>Previous treatments / exposures</td>
<td>Radiotherapy, chemotherapy -&gt; MDS, AML</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol, benzol, SAA or MDS/AML</td>
</tr>
<tr>
<td>Drugs</td>
<td>Toxic effect</td>
</tr>
<tr>
<td>Chronic alcohol abuses</td>
<td>Hepatopathy</td>
</tr>
<tr>
<td>Pain crisis, black urine crisis</td>
<td>Paroxysmal nocturnal hemoglobinurie (PNH)</td>
</tr>
<tr>
<td>Bleeding, infections</td>
<td>Estimation of the degree of pancytopenia</td>
</tr>
<tr>
<td></td>
<td>Eventually additional hemostatic problems</td>
</tr>
</tbody>
</table>
# Clinical findings of the patient

<table>
<thead>
<tr>
<th>Findings</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>Lymphoma, Hodgkin lymphoma but also viral infection</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Usually not found in MDS or SAA. Typical in MPN, MDS/MPN, CMML. Sometimes found in acute leukemia. Lymphoma, Hodgkin disease but also in hepatopathy with portal hypertension.</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>MPN, CMML. Lymphoma, Hodgkin disease. But also in hepatopathy with portal hypertension.</td>
</tr>
<tr>
<td>Mediastinal bulk</td>
<td>Lymphoma, Hodgkin disease. T-ALL.</td>
</tr>
<tr>
<td>Excessive bleedings</td>
<td>When platelets are &gt; 30 x10^9/L.</td>
</tr>
<tr>
<td></td>
<td>▪ functional platelet defect, Aspirin.</td>
</tr>
<tr>
<td></td>
<td>▪ Additional hemostasis problem (antibodies against coagulation factors).</td>
</tr>
</tbody>
</table>
Blood counts and blood films

- Degree of cytopenia
- RDW
- Immature precursors
- Presence of blasts
- Howell Jolly
- Dysplasia of neutrophils
- Abnormal platelets
- Duration of abnormalities

RDW <14%
RDW = 21%
# Systematic bone marrow examination

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Occurrence</th>
</tr>
</thead>
</table>
| Cellularity | Increased in MPN, and usually in MDS  
Dry tap of aspiration in MPN, sometimes in ALL  
Aplastic in SAA, hypoplastic MDS/AML |
| Erythropoiesis | None in erythroaplasia  
Dysplastic in MDS, some AML, sometimes in SAA  
Increased, morphologically normal in hemolysis |
| Myelopoiesis | Dominating, morphologically normal in MPN  
Dysplastic in MDS |
| Blasts      | Counting for MDS/AML  
CD34+ equivalent |
| Megakaryopoiesis | Dysplastic in MDS, sometimes in AML  
Different type of abnormalities in MPH (histology) |
| Other cells | Reed Sternberg and Hodgkin cells (Histology)  
Cancer cells  
Others |
| Conclusions | No longer a description  
Conclusion of the examination / diagnosis if possible |
Main causes of medical errors in hematological diagnostics

- Incomplete information on the case
- Bad quality of the material
  - blood films, aspirates, biopsies, colorations
- No integrated diagnosis
  - Speak together
- Confirmatory bias
  - To seek data that confirm a favorite hypothesis and to interpret even the low-relevance data as being supportive of a hypothesis
  - we want make the diagnosis
Thanks for your attention