Normocytic Anemia: Aplastic Anemia (Bone Marrow Aplasia) — Primary and Secondary Causes

If not treated the aplastic anemia diseases leads to death. Everything you have to know as a future physician in this article.

Definition of Aplastic Anemia

Aplastic anemia is a type of anemia that involves reduced hematopoiesis and is caused by a maturation defect in the pluripotent, hematopoietic stem cells. The underlying cause is bone marrow failure, which is distinguished from other bone marrow diseases by a cell count of the bone marrow of under 25 %, i.e., by a marked hypoplasia or aplasia of the bone marrow.
Etiology and Pathogenesis of Aplastic Anemia

The exact cause of aplastic anemia has not yet been definitively confirmed, which is why about half of all disease cases are classified as idiopathic. The only identified fact regarding its pathogenesis is that this disorder has a direct link to a high reduction in the number of pluripotent, hematopoietic stem cells. Beyond that, an autoimmune reaction that affects the T-cells is being discussed as a likely explanation.

The disease can be divided into congenital (primary) and acquired (secondary) causes:

<table>
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<tr>
<th>Primary Causes</th>
<th>Secondary Causes</th>
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<tbody>
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<td>Blackfan-Diamond anemia, Fanconi anemia</td>
<td>Medication, chemicals (benzene), ionizing radiation, infections, autoimmune disease, heavy metals</td>
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Congenital Aplastic Anemia (Primary Form)

Fanconi Anemia

Fanconi anemia is a disorder of autosomal-recessive inheritance and can be subdivided into seven subtypes, however, it will not be our subject in this article. The disease usually manifests at the age of 5 to 10 years. The underlying cause is assumed to be a DNA repair defect. It can manifest in form of microcephaly, absence of radii or thumbs, pelvic or horseshoe kidney, hyperpigmentation or hypopigmentation of the skin, and in some rare cases even mental retardation.

Image: “Clinical manifestations of representative FA patients. A: Hexadactylysm; B: Absence of right hand thumb; C: Café au lait spots.” by openi. License: CC BY 2.0

The treatment of choice is a bone marrow transplant. Furthermore, treatment with androgens is also an option; however, the side-effects can be considerable (virilization, liver anomalies), and the remission that is capable of being achieved lasts only for about 2 years.
Blackfan-Diamond Anemia

Blackfan-Diamond anemia is the hereditary form of pure red-cell aplasia. It involves a primary erythroid aplasia in the bone marrow which doesn't affect any other cell lines. Unlike with other forms of aplastic anemia, it does not involve pancytopenia.

The leukocyte and thrombocyte numbers are in the normal range. However, the erythroblasts in the bone marrow are markedly reduced or are not present at all. Clinical manifestations can be observed in infants and present themselves as typical symptoms of anemia. In addition, multiple somatic dysmorphias like genital malformations or dysphalangia develop.

Treatment consists of the administration of glucocorticoids and possibly carrying out a bone marrow transplant.

Acquired Aplastic Anemia (Secondary Form)

Acquired aplastic anemia is usually as a result of direct damage to the hematopoietic bone marrow. Factors known to negatively impact the bone marrow are mainly radiation and medication capable of causing cytotoxic effects. In addition, chemical substances like benzene disturb the functioning of the bone marrow. Furthermore, viral infections can lead to the development of aplastic anemia.

However, it is not always possible to find a causative factor. For instance, the acquired chronic form of pure red-cell aplasia cannot always be traced back to any of the above mentioned causes.

Pure Red-Cell Aplasia

Chronic Acquired Form of Pure Red-Cell Aplasia

Pure red-cell aplasia is a rare syndrome that can be inherited (see Blackfan-Diamond syndrome) or secondarily acquired. Unlike most of the other forms of aplastic anemia, the chronic form of pure red-cell aplasia does not involve pancytopenia. Only the number of the erythroblasts is markedly reduced. It is thus an isolated aplasia of erythropoiesis.

Since in many cases, the causative factor cannot be determined, most cases are classified as idiopathic. But it can also develop within the scope of an autoimmune disease such as systemic lupus erythematosus (SLE).

Treatment of the acquired red-cell aplasia is similar to that of the congenital form. It can be treated with corticosteroids as well as with immunosuppressants.

Acute Transient Form of Pure Red-Cell Aplasia

The acute transient form of pure red-cell aplasia refers to a temporary aplastic impairment of erythropoiesis that is usually caused by parvoviruses or certain drugs.

Drug-Induced Aplastic Anemia

A series of cytotoxic medications is known to increase the risk of developing aplastic anemia. Here, an important distinction should be made: antimetabolites such as methotrexate and mitotic inhibitors like daunorubicin both only provoke temporary aplasia, while alkylating agents like busulfan cause chronic aplasia.
Furthermore, non-cytotoxic medications such as chloramphenicol or gold can cause an aplastic anemia. Since the incidence with chloramphenicol is very high, this drug should only be given for very severe cases after all other medication has failed.

Medication that can cause damage to the bone marrow includes the following:

- Cytostatic agents
- Sulfonamides
- Chloramphenicol
- NSAIDs
- Phenylbutazone
- Gold preparations
- Colchicine

**Chemical Substances**

Chemical substances that are known to provoke damage to the bone marrow are:

- Benzene
- Hair dye products
- Insecticides

**Ionizing Radiation**

Bone marrow failure can also occur as a consequence of radiation therapy. Therefore, when there is suspicion of bone marrow failure, the medical history should take into account previous radiological examinations.

**Autoimmune Diseases**

Since there is an etiological relation between aplastic anemia and autoimmune reactions, the correlation of certain autoimmune diseases with the development of aplastic anemia does not come as a surprise. Autoimmune diseases that are capable of causing an increased risk of developing aplastic anemia are:

- **Systemic lupus erythematosus (SLE)**
- Graft versus host disease (GVHD)

**Viral Infections**

The viruses which are proven to have an influence on the development of aplastic anemia are:

- Parvovirus B19
- **HIV virus** (AIDS)
- Hepatitis viruses A and C
- Epstein-Barr virus (EBV)
- Cytomegalovirus (CMV)

**Symptoms and Clinical Presentation of Aplastic Anemia**

Aplastic anemia can have an **insidious** or an **acute** onset. The first warning signs may be neutropenia or thrombocytopenia. In addition, there are typical clinical signs of anemia, such as **fatigue, exhaustion**, overall weakness, **pale skin and pale mucous membranes**. There is also an increased occurrence of infections, especially in the mouth and cervical areas, and an increased bleeding tendency (epistaxis, menorrhagia).
Diagnosis and Differential Diagnosis of Aplastic Anemia

Since pancytopenia is typical of aplastic anemia, this finding should prompt (after excluding other more probable diseases) further investigation directed towards possible bone marrow failure. Before that, the following diseases associated with pancytopenia have to be considered during differential diagnoses:

- Myelodysplastic syndrome (MDS)
- Acute myeloid leukemia (AML)
- Megaloblastic anemia
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Temporary pancytopenia after viral infections

Besides pancytopenia, the blood count will show a normochromic, normo-, or macrocytic anemia. The reticulocyte count will be reduced. Serological examinations of the blood should look for parvovirus B 19, hepatitis virus, Epstein-Barr viruses, and cytomegaloviruses.

The actual confirmation of the cause is done by examining the bone marrow (trephine biopsy and aspiration). The cells taken from the iliac crest are examined cytologically and histologically. The detection of hypoplasia or aplasia of the hematopoietic marrow is to be expected due to it being replaced by non-hematopoietic fatty bone marrow. Also, the absence of precursor cells of other cell lines is another characteristic.

Treatment of Aplastic Anemia

When aplastic anemia is suspected, the causative factor of the anemia (radiation, chemicals, medication etc.) should be identified as a first step. The only promising and curative treatment, however, involves allogeneic stem cell transplantation (age < 40 years), which is aimed at generating a completely new hematopoiesis.

During treatment, it is of great importance that as few as possible transfusions are performed before stem cell transplantation is carried out because every transfusion could lead to alloimmunization of the patient and thus decrease the chances of success of a transplantation. Possible donors are siblings, and if they are not available, unrelated donors (in both cases, having at least 10 HLA alleles should be a match).
Prognosis for Aplastic Anemia

If stem cell transplantation is done early, prognosis is good with a relatively low risk of recurrence. Patients treated with immunosuppressants, however, have an increased risk of recurrence with every third patient experiencing a relapse. In addition, there is an increased risk for these patients to develop, over the following years, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or a paroxysmal nocturnal hemoglobinuria (PNH).

If left untreated, aplastic anemia is lethal in 75% of the cases.

References


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