The Pancytopenias

The Inherited Pancytopenias

Pancytopenia refers to a reduction below normal values of all 3 peripheral blood component: leukocytes, platelets, and erythrocytes. Pancytopenia requires microscopic examination of a bone marrow biopsy specimen and a marrow aspirate to assess overall cellularity and morphology. There are 3 general categories of pancytopenia depending on the marrow findings.
INHERITED PANCYTOPENIA SYNDROMES

Fanconi anemia
Shwachman-Diamond syndrome
Dyskeratosis congenita
Congenital amegakaryocytic thrombocytopenia
Unclassified inherited bone marrow failure syndromes
Other genetic syndromes  Down syndrome
Dubowitz syndrome
Seckel syndrome
Reticular dysgenesis
Schimke immunoosseous dysplasia
Familial aplastic anemia (non-Fanconi)
Cartilage-hair hypoplasia
Noonan syndrome
Fanconi Anemia •

Etiology and Epidemiology •

Fanconi anemia (FA) is primarily inherited in an autosomal recessive manner (one uncommon form is X-linked recessive). It occurs in all racial and ethnic groups. At presentation, patients with FA may have: (1) typical physical anomalies but normal hematologic findings; (2) normal physical features but abnormal hematologic findings; or (3) physical anomalies and abnormal hematologic findings, which constitute the classic phenotype (39% of cases).

Approximately 75% of patients are 3-14 yr of age at the time of diagnosis.
Pathology

Patients have abnormal chromosome fragility, which is seen in metaphase preparations of peripheral blood lymphocytes cultured with phytohemagglutinin and enhanced by adding clastogenic agents such as diepoxybutane (DEB) and mitomycin C. Cell fusion of FA cells with normal cells or with cells from some unrelated patients with FA produces a corrective effect on chromosomal fragility, a process called complementation.
Therefore, mutant gene proteins lead to genomic instability, chromosome fragility, and FA. An inability of FA cells to remove oxygen-free radicals, resulting in oxidative damage, is a contributing factor in the pathogenesis.
Clinical Manifestations

The most common anomaly in FA is hyperpigmentation of the trunk, neck, and intertriginous areas, as well as Cafe-au-lait spots and vitiligo, alone or in combination. Half the patients have short stature. Growth failure may be associated with abnormal growth hormone secretion or with hypothyroidism. Absence of radii and thumbs that are hypoplastic, bifid, or absent are common. Anomalies of the feet, congenital hip dislocation, and leg abnormalities are seen.
A male patient with FA may have an underdeveloped penis; undescended, atrophic, or absence of the testes; and hypospadias or phimosis. Females can have malformations of the vagina, uterus, and ovary. Many patients have a FA “facies,” including microcephaly, small eyes, epicanthal folds, and abnormal shape, size, or positioning of the ears. Ectopic, pelvic, or horseshoe kidneys are detected by imaging and may show other organs as duplicated, hypoplastic, dysplastic, or absent kidneys. Cardiovascular and gastrointestinal malformations also occur. Approximately 10% of patients with FA are cognitively delayed.
Laboratory Findings

Marrow failure usually ensues in the 1st decade of life. Thrombocytopenia often appears initially, with subsequent onset of granulocytopenia and then macrocytic anemia. Severe aplasia develops in most cases, but its full expression is variable and evolves over a period of months to years. The marrow becomes progressively hypocellular and fatty, like that in severe acquired aplastic anemia.
Chromosome fragility is indicated by spontaneously occurring chromatid breaks. For prenatal diagnosis, abnormal chromosome breakage can be tested for in amniotic fluid cells or in tissue from a chorionic villus biopsy.
Complications
A major feature of the phenotype of FA is the propensity for cancer. The most frequent solid tumors are squamous cell carcinomas of the head, neck, and upper esophagus, followed by carcinomas of the vulva and/or anus, cervix, and lower esophagus.

Human papilloma virus is suspected in the pathogenesis. Benign and malignant liver tumors occur (adenomas, hepatomas) and are usually associated with androgen therapy for aplastic anemia.

Androgens are also implicated in the etiology of peliosis hepatis (blood-filled hepatic sinusoids).
Diagnosis

FA should be considered in all children and young adults with unexplained cytopenias. Abnormal hematologic findings and characteristic physical anomalies suggest the diagnosis, which is confirmed with a lymphocyte chromosomal breakage study using DEB.
Most patients have stable elevations of serum α-fetoprotein, independent of liver complications or androgen therapy. The laboratory measurement of serum α-fetoprotein can be used as a rapid screening diagnostic test. Specialized laboratories can perform an accurate diagnostic and mutant gene subtyping assay, whereby patient lymphocytes or fibroblasts are studied after exposure to mitomycin C.
Treatment

A hematologist and a team should supervise patients with FA. If the hematologic findings are stable and there are no transfusion requirements, observation is indicated. Subspecialty consultations for anomalies and disabilities can be arranged during this interval. If growth velocity is below expectations, endocrine evaluation is needed to identify growth hormone deficiency or hypothyroidism. Screening for glucose intolerance and hyperinsulinemia should be performed annually or biannually, depending on the degree of hyperglycemia found on initial testing.
Blood counts should be performed every 1-3 mo; bone marrow aspiration and biopsy are indicated annually for leukemia.

Patients should be assessed for solid tumors at least annually.

Beginning at menarche, female patients should be screened annually for gynecologic cancer.

Administration of human papilloma virus quadrivalent vaccine to prevent squamous cell carcinoma will likely become a standard intervention.
Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for the hematologic abnormalities. Patients with FA <10 yr old who undergo transplantation using an HLA–identical sibling donor have a survival rate >80%. Survival rates are lower for patients undergoing the procedure when >10 yr.
Granulocyte colony-stimulating factor (G-CSF) can usually induce an increase in the absolute neutrophil count and occasionally may boost platelet counts and hemoglobin levels.
Androgens produce a response in 50% of patients, heralded by reticulocytosis and a rise in hemoglobin within 1-2 mo. White blood cell counts may increase next, followed by platelet counts, but it may take many months to achieve the maximum response.
The premise for gene therapy in FA is based on the assumption that corrected hematopoietic cells offer a growth advantage.
Prognosis

From FA cases reported in the 1990s, the projected median survival was >30 yr of age, an improvement over that in the previous decade. Successes with HSCT have dramatically improved the outlook. Careful surveillance for known complications, especially cancer, and prompt intervention on their detection has also contributed to the improved survival.
The Acquired Pancytopenias
Etiology and Epidemiology

Drugs, chemicals, toxins, infectious agents, radiation, and immune disorders can result in pancytopenia by direct destruction of hematopoietic progenitors, disruption of the marrow microenvironment, or immune-mediated suppression of marrow elements. A careful history of exposure to known risk factors should be obtained for every child presenting with pancytopenia. Even in the absence of the classic associated physical findings, the possibility of a genetic predisposition to bone marrow failure should always be considered. The majority of cases of acquired marrow failure in childhood are “idiopathic,” in that no causative agent is identified. These are probably immune-mediated through activated T lymphocytes and cytokine destruction of marrow progenitor cells.
ETIOLOGY OF ACQUIRED APLASTIC ANEMIA

Radiation drugs and chemicals:
   Predictable: chemotherapy, benzene
   Idiosyncratic: chloramphenicol, antiepileptics, gold; 3,4-methylenedioxyamphetamine

Viruses:
   Cytomegalovirus
   Epstein-barr
   Hepatitis b
   Hepatitis c
   Hepatitis non-A, non-B, non-C (seronegative hepatitis)
   HIV

Immune diseases:
   Eosinophilic fasciitis
   Hypoimmunoglobulinemia
   Thymoma

Pregnancy

Paroxysmal nocturnal hemoglobinuria

Marrow replacement:
   Leukemia
   Myelodysplasia
   Myelofibrosis

Autoimmune
Pathology and Pathogenesis

The hallmark of aplastic anemia is peripheral pancytopenia, coupled with hypoplastic or aplastic bone marrow. The severity of the clinical course is related to the degree of myelosuppression. Severe aplastic anemia is defined as a condition in which 2 or more cell components have become seriously compromised (absolute neutrophil count [ANC] <500/mm$^3$, platelet count <20,000/mm$^3$, reticulocyte count <1% after correction for hematocrit) in a patient whose bone marrow biopsy material is moderately or severely hypocellular.
Approximately 65% of patients who first present with moderate aplastic anemia (ANC 500-1,500/mm³, platelet count 20,000-100,000/mm³, reticulocyte count <1%) eventually progress to meet the criteria for severe disease if they are simply observed. Bone marrow failure may be a consequence of a direct cytotoxic effect on hematopoietic stem cells from a drug or chemical or may result from either cell-mediated or antibody-dependent cytotoxicity.
Clinical Manifestations, Laboratory Findings, and Differential Diagnosis

Pancytopenia results in increased risks of cardiac failure, infection, bleeding, and fatigue. Acquired pancytopenia is typically characterized by anemia, leukopenia, and thrombocytopenia in the setting of elevated serum cytokine values. Other treatable disorders, such as cancer, collagen vascular disorders, PNH, and infections that may respond to specific therapies (IV immune globulin for parvovirus), should be considered in the differential diagnosis.
Careful examination of the peripheral blood smear for RBC, leukocyte, and platelet morphologic features is important. A reticulocyte count should be performed to assess erythropoietic activity. In children, the possibility of congenital pancytopenia must always be considered, and chromosomal breakage analysis should be performed to evaluate for Fanconi anemia. The presence of fetal hemoglobin suggests congenital pancytopenia but is not diagnostic. Bone marrow examination should include both aspiration and a biopsy, and the marrow should be carefully evaluated for morphologic features, cellularity, and cytogenetic findings.
Treatment

The treatment of children with acquired pancytopenia requires comprehensive supportive care coupled with an attempt to treat the underlying marrow failure. For patients with an HLA-identical sibling marrow donor, allogeneic bone marrow transplantation (BMT) offers a 90% chance of long-term survival. The risks associated with this approach include the immediate complications of transplantation, graft failure, and graft versus host disease. Late adverse effects associated with transplantation may include secondary cancers, cataracts, short stature, hypothyroidism, and gonadal dysfunction. Only 1 in 5 patients has an HLA-matched sibling donor, so matched-related BMT is not an option for the majority of patients.
For patients without a sibling donor, the major form of therapy is immunosuppression with antithymocyte globulin (ATG) and cyclosporine, with a response rate of 60-80%.
For patients who show no response to immunosuppression or who experience relapse after immunosuppression, matched unrelated donor marrow/stem cell transplant is a treatment option, with a response rate approaching 80% in later studies.
Complications

The major complications of severe pancytopenia are predominantly related to the risk of life-threatening bleeding from prolonged thrombocytopenia or to infection secondary to protracted neutropenia. Patients with protracted neutropenia due to bone marrow failure are at risk not only for serious bacterial infections but also for invasive mycoses. The general principles of supportive care that have evolved from the use of chemotherapy-related myelosuppression to treat patients with cancer should be fully extended to the care of patients with acquired pancytopenia.
**Prognosis**

Spontaneous recovery from pancytopenia rarely occurs. If left untreated, severe pancytopenia has an overall mortality rate of approximately 50% within 6 mo of diagnosis and of >75% overall, with infection and hemorrhage being the major causes of morbidity and mortality. The majority of children with acquired severe aplastic anemia show response to allogeneic marrow transplantation or immunosuppression, leaving them with normal or near-normal blood cell counts.