**Congenital anemic syndromes**

**Hereditary spherocytosis (HS)**
A congenital anemia caused by abnormal cytoskeletal proteins of red blood cells that result in deformed red cell membrane and hemolysis
Most common hereditary red cell membrane disorder and most common congenital hemolytic anemia (incidence 1:2000)
Clinically presented with variable degrees of anemia, jaundice, splenomegaly, biliary obstruction, splenomegaly
**Blood:** Normocytic normochromic anemia, increased reticulocytes, spherocytes are smaller than normal red cells but MCV may be normal (due to increased reticulocytes)
**Morphology:** Nearly all red blood cells are spherocytes
**Bone marrow:** Normocellular or hypercellular, erythroid hyperplasia
**Lab:** Evidence of hemolysis: Anemia, high LDH, low haptoglobin, high direct bilirubin, increased osmotic fragility of red cells
**Genetics:** Mutations of one of the genes: ANK1 (most common), SLC4/A1, SPTB, SPTA, EPB41, EPB42
**Differential:** Hereditary elliptocytosis (HE) and hereditary poikilocytosis (HP):
Congenital anemias due to mutations of cytoskeletal protein genes (most common SPTA), less frequent than HS (incidence 1:5000)
**HE:** No or mild hemolytic anemia, increased spherocytes on blood smear
**HP:** Severe anemia and hemolysis, increased poikilocytes on blood smear
**Treatment:** Transfusion, splenectomy

**Glucose-6-phosphate dehydrogenase deficiency (G6PD)**
A red blood cell enzymatic disorder caused by mutations of G6PD gene resulting in deficiency of G6PD and hemolytic anemia
Most common red cell enzymatic disorder (affects 4 million people worldwide)
X-linked recessive inheritance
Clinically presented with hemolytic anemia when exposed to oxidative drugs or fava bean, recovers when stress is removed
**Blood:** Hemolytic anemia when exposed to offending agents, polychromasia, some schistocytes, characteristic “bite cells”, Heinz body
**Bone marrow:** Non-specific
**Lab:** Normocytic and macrocytic anemia, high reticulocytes, high LDH
**Blood smear:** Polychromasia, bite cells, schistocytes, Heinz body
**Genetics:** Mutations of G6PD gene
**Diagnosis:** Blood smear review and lab tests, enzymatic activity analysis
**Differential:** Pyruvate kinase dehydrogenase deficiency: Autosomal recessive inheritance, hemolytic anemia
**Treatment:** Removal of offending agents

**Diamond-Blackfan anemia (DBA)**
A congenital anemia present at birth or during infancy, associated with short stature and various craniofacial and thumb abnormalities
Incidence: One new case per million children
Inheritance: sporadic (majority), autosomal dominant, autosomal recessive

**Blood:** macrocytic anemia (MCV 110-140)
**Bone marrow:** marked to absent erythropoiesis, increased hematogones, preserved myelopoiesis and megakaryopoiesis
**Lab:** anemia, macrocytic red cells, low reticulocytes, increased hemoglobin F, express i antigen on RBC, increased RBC adenosine deaminase
**Genetics:** linkage to 19q13.2 region mutations (ribosome protein S19 gene)
**Differential:** *Transient erythroblastopenia of childhood (TEC)*
  *Parvovirus-related erythroblastopenia*

**Treatment:** most patients respond to steroids

**Congenital dyserythropoietic anemia (CDA)**
A group of congenital disorders characterized by effective erythropoiesis and dysethropoiesis in bone marrow red cell precursors
Inheritance: Type I and II: autosomal recessive, Type III: autosomal dominant or sporadic
May present at any age during childhood
Clinically presented with various degrees of macrocytic or normocytic anemia
Associated abnormalities: skeletal defect, skin hypopigmentation (type I), visual defect, mental retardation (type III)

**Blood:** Normocytic or macrocytic anemia, moderately anisopoikilocytosis, prominent basophilic stippling
**Bone marrow:** Striking erythroid hyperplasia and prominent dyserythropoiesis (consistent finding). Characteristic features:
  - Type I: Nuclear bridging
  - Type II: Binucleation
  - Type III: Giant erythroblasts

**Lab:** Anemia, normal or mild increase of reticulocytes
**Genetics:** Genetic mutations: Type I: \( CDAN1 \) gene, Type II: \( SEC23B \) gene, Type III: \( KIF23 \) gene
**Differential:** *Myelodysplastic syndrome*
**Treatment:** Transfusion, chelating therapy, splenectomy, gene therapy

**Congenital thrombocytopenic syndromes**

**Wiskott-Aldrich syndrome (WAS)**
**Definition:** X-linked recessive disease characterized by thrombocytopenia, immunodeficiency, and eczema
Affects only male children
Clinically presented as eczema, bloody diarrhea, petechiae, bruising, nose bleeding, ear and sinus infection, autoimmune disorders
Leukemia or lymphoma develop in one third patients: AML, MDS, DLBCL, LyG, cHL

**Blood:** Thrombocytopenia, small platelets, eosinophilia in some patients. Serum IgM low, IgA high, IgE normal or high, IgG variable
**Bone marrow:** Indicated to rule out leukemia and lymphoma
**Lab:** Mutation analysis by sequencing WAS gene
**Genetics:** WAS gene mutations in all patients, Function of WAS protein is to activate actin polymerization b serving as a nucleation-promoting factor for the Arp2/3 complex, which generates branched actin filaments
Differential: **TAR syndrome** (Thrombocytopenia with absent radii): Congenital disorder with thrombocytopenia and absence of radius radius). Caused by double mutations of 1q21.1 deletion (inherited) and **RBM8A** mutation

**MYH9 related disease**: Discussed in lesson 2

**Treatment**: Mitigates symptoms and complications, IVIG, stem cell transplant, gene therapy

### Congenital neutropenic syndromes

**Schwachman-Diamond syndrome (SDS)**

Definition: An autosomal recessive disorder characterized by neutropenia, exocrine pancreatic insufficiency, short stature, and growth retardation

Usually presented with malabsorption (pancreatic exocrine dysfunction, mimic cystic fibrosis), infection (neutropenia), and less commonly skeletal detects (such as deformed rib cage)

**Blood**: Neutropenia without morphologic abnormalities

**Bone marrow**: Granulocytic hypoplasia

**Lab**: Isolated neutropenia by CBC

**Genetics**: Mutations of **SBDS** gene located at chromosome 7q11. Mechanism includes gene conversion (copy of mutated, non-functional **SBDS** pseudogene) that aberrantly recombines at meiosis, resulting in incorporation of pseudogene sequences into functional copy and inactivates **SBDS** gene

**Differential**: **Kostman syndrome**: aka severe congenital neutropenia. Autosomal dominant or recessive disorders involving mutations of one of the 6 genes (**ELANE** and others).

Presented with infection at early infancy. Neutropenia in blood and agranulocytosis in bone marrow. Respond to GCSF

**Chediak-Higashi syndrome (CHS)**: Autosomal recessive disorder involving defect of lysosomal trafficking regulator proteins (encoded by **CHS1** gene), resulting in defect in phagocytosis. Presented with recurrent infection, albinism, peripheral neuropathy. Large lysosomal granules in neutrophils, monocytes, and lymphocytes on blood smear. No specific treatment

### Congenital bone marrow failure syndromes

**Fanconi anemia**

Autosomal recessive disorder with progressive bone marrow failure, mental retardation, and multiple bone, skin, renal abnormalities

Severity of disease highly variable from mild to severe, 90% progress to bone marrow failure by 40 years of age

Higher frequency in Ashkenazi Jews and Afrikaners in South Africa

Cytopenia usually starts from infancy (thrombocytopenia first), with slow progression to severe pancytopenia in mid-to-late childhood

Hematologic symptoms: petechiae, pale and fatigue, infection

High risk of progression to myelodysplastic syndrome and acute myeloid leukemia

**Blood**: Macrocytic anemia, thrombocytopenia, neutropenia

**Bone marrow**: Early stage: normocellular or hypercellular with megaloblastic erythropoiesis.

Late stage: progressive pancytopenia to eventually acellular

**Lab test**: pancytopenia, high MCV, increased fetal hemoglobin, express i antigen on RBC

**Genetics**: Defect proteins on DNA repair via homologous recombination involving mutations of 22 **FA** or **FA-like** genes (**FANCA**, **FANCB**, etc)

**Prognosis**: 15%-20% develop MDS and AML
Treatment: Growth factors, stem cell transplant
Differential: **Dyskeratosis congenita**: An X-linked recessive disorder associated with skin, nail, mucosal abnormalities, gradual worsening of pancytopenia, eventual aplasia in >50%, mental retardation, internal organ abnormalities, increased risk of squamous cell carcinoma
**Sideroblastic anemia**: A congenital or acquired red blood cell disorder characterized by sideroblasts in bone marrow and anemia due to ineffective erythropoiesis, variable inheritance patterns in congenital forms (most common X-linked), drug induced in acquired forms, treated with pyridoxine, transfusion, splenectomy

### Lysosomal storage diseases

**Gaucher disease**
Autosomal recessive disorder caused by deficiency of enzyme glucocerebrosidase resulting in accumulation of insoluble glucocerebroside in lysosomes of histiocytes and neurons in CNS
Clinically presented with bruising, fatigue, hepatosplenomegaly
**Blood**: Pancytopenia
**Three subtypes: Type 1** (adult or nonneuropathic type): >90% cases, mainly affects Ashkenazi Jews, mild form affecting adults, hepatosplenomegaly
**Type 2** (acute neuropathic type): Affects small children, fulminant CNS disease and death by 2 years of age
**Type 3** (Juvenile or subacute neuropathic type): Later onset of CNS symptoms and longer disease course, mainly affects Swedish people
**Morphology**: Accumulation of histiocytes in bone marrow, liver, spleen, and other organs.
Histiocytes have abundant “tissue paper” type cytoplasm and small round nuclei. “Gaucher cells” identified by PAS stain
**Diagnosis**: Enzyme testing, genetic testing
**Treatment**: Enzyme replacement therapy

**Niemann-Pick disease**
Autosomal recessive disorder caused by deficiency of enzyme sphigomyelinase resulting in accumulation of sphigomyelin in lysosomes of histiocytes and neurons in CNS
Clinically presented with reduced appetite, abdominal extension and pain, ataxia, dysarthria, dysphagia, dystonia, gaze palsy. Dementia and seizure in more severe cases
**Three subtypes: Type A**: Histiocytes accumulate in both viscera and neurons, infantile
**Type B**: Histiocytes only accumulate in viscera
**Type C**: Most common type, variable age of onset and neurologic disease
**Morphology**: Accumulation of histiocytes in bone marrow, liver, spleen, and other organs.
Histiocytes have abundant “formy” type cytoplasm and small round nuclei, “Sea-blue” histiocytes in bone marrow aspirate
**Diagnosis**: Enzyme testing, genetic testing (*SMPD1, NPC1, NPC2* genes)
**Treatment**: Manages symptoms, no specific treatment
**Prognosis**: Type A: fatal by the age of 2 years. Types B and C: better prognosis

**Juvenile xanthogranuloma (JXG)**
Definition: Benign idiopathic cutaneous histiocytic lesion affecting primarily children
Infants most common, may also affects older children and adults, median age 2 years
Orange red macules or papules, single or multiple, usually on face neck and upper trunk
Ocular lesions (in ~10% of JXG) may affect vision
Deeper organ involvement in rare cases
JXG often coexists with neurofibromatosis type 1, juvenile chronic myelomonocytic leukemia

**Morphology:** Expansile lesion in dermis sparing epidermis
Variable number if benign appearing histiocytes, mixed with Touton type giant cells, lymphocytes, fibroblasts

**Histologic variants:**
- **Typical type:** Vacuolated histiocytes, Touton giant cells
- **Xanthogranuloma type:** Foamy histiocytes, rare or absent Touton giant cells
- **Fibrohistiocytic type:** Spindle and fusiform cells, collagen background

**Phenotype:** CD68+, factor VIII+, LCA+, S-100-, CD1a-, Langerin-

**Genetics:** Unknown

**Prognosis:** Cutaneous lesions: self-limited, resolves in one to five years
Ocular lesions: do not resolve spontaneously, requires surgical intervention

**Differential:** Langerhans cell histiocytosis, molluscum contagiosum, hemangioma, neurofibroma

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**Langerhans Cell Histiocytosis (LCH)**
Discuss in lesson 21

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**Juvenile chronic myelomonocytic leukemia (JMML)**
Definition: clonal hematopoietic disease of childhood with proliferation of predominantly monocytes and granulocytes
Accounts for 2-3% childhood leukemia, 20-30% of MDS and MPN in children
75% in children <3 years, boys:girls 2:1
Sites of involvement include blood, bone marrow, spleen, liver. Can also involve GI, pulmonary, skin, lymph nodes
Clinically presented with constitutional symptoms, hepatosplenomegaly, GI and respiratory symptoms, bleeding, skin rash. Usually not involves CNS
Associated with Noonan syndrome-like disorder (15%) and neurofibromatosis type 1 (10%)

**Blood:** Proliferation of neutrophils and precursors, and mature monocytes, anemia and thrombocytopenia. Increased hemoglobin F level, hypergammaglobulinemia, increased autoantibodies

**Bone marrow:** Hypercellular with predominantly myeloid proliferation, various degree of monocytic proliferation (typically 5-10%). Absent significant dysplasia, blasts <20%

**Phenotype:** Increased granulocytic and monocytic cells. No specific phenotypic aberrancy

**Genetics:** 85% cases have one of the 5 RAS pathway mutations-RASopathies (PTPN11, NRAS, KRAS, NF1, CBL)

**Prognosis:** Unfavorable factors: PTPN11 mutations, KRAS and NRAS mutations, Co-occurs with NF-1. Favorable factors: RALD, germline CBL mutations

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**Diagnostic criteria for JMML (must meet criteria 1 and 2 or criteria 1 and 3)**

1. **Clinical and hematologic criteria (all required)**
   - Monocyte count in blood ≥1x10⁹/L
   - Blasts in blood and marrow <20%
   - Splenomegaly
   - No Ph chromosome or BCR-ABL1

2. **Genetic criteria (requires any 1 criterion)**
   - Somatic mutations in PTPN11, KRAS, or NRAS
   - Neurofibromatosis type 1 or NF1 mutation
   - Germline CBL mutation and loss of heterozygosity of CBL
3. Other criteria (cases do not meet the genetic criteria must meet following criteria)
   Monosomy 7 or other chromosome abnormalities
   or
   ≥2 of the following:
   - Increased hemoglobin F
   - Myeloid or erythroid precursors in blood
   - GMCSF (aka CSF2) hypersensitivity by colony assay
   - STAT5 hyperphosphorylation

**Transient myeloproliferative disorder of Down syndrome (TMD)**
Transient proliferation of myeloblasts in blood and bone marrow in infants with Down syndrome
- Affects 10% newborn with Down syndrome
- Asymptomatic and self-limited, blasts usually clear within 3 months of birth
- **Blood:** Leukocytosis, usually mild, no significant anemia or thrombocytosis. Leukoeoerythroblastosis common. Percentage of blasts varies. Heterogeneous blast morphology
- **Bone marrow:** Percent of blasts is usually lower than blood
- **Phenotype:** Myeloid blasts phenotype, megakaryocytic differentiation (at least in a portion of blasts) in nearly all cases
- **Genetics:** Trisomy 21, One third patients have additional cytogenetic abnormalities
- **Prognosis:** Self-limited
- **Differential:** Acute myeloid leukemia

<table>
<thead>
<tr>
<th><strong>Comparison of TMD and AML in Down syndrome</strong></th>
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<tbody>
<tr>
<td><strong>TMD</strong></td>
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<tr>
<td>Usually asymptomatic</td>
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<tr>
<td>No cytopenia</td>
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<tr>
<td>Heterogeneous blast morphology</td>
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<tr>
<td>Percent blasts: blood &gt; marrow</td>
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<tr>
<td>Average age of onset 7.4 days</td>
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<td>CD11b+/-, CD13 +/-</td>
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<td>Spontaneous remission</td>
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**B-lymphoblastic leukemia/lymphoma (B-ALL)**

**B-lymphoblastic leukemia/lymphoma with t(v;11q23)**
- B-ALL with translocation involving KMT2A (MLL) translocation with various partners
- Most common infantile leukemia (also affects adults), less common in older children
- Clinically present with very high white count, high frequency of CNS involvement
- **Morphology:** Typical lymphoblast morphology
- **Phenotype:** Pro B type (CD10-, CD19+, CD24-)
- **Genetics:** Translocations of KMT2A at 11q23.3 involve >100 fusion partners. Most common types include t(4;11) AFF1-KMT2A, t(9;11) MLLT3-KMT2A, t(11;19) KMT2A-MLLT1
- Usually KMT2A is the sole abnormality
- **Prognosis:** Poor prognosis if < 6 months of age or t(4;11)
**B-lymphoblastic leukemia/lymphoma with t(12;21) ETV6-RUNX1**
B-ALL with translocation involving ETV6 (TEL) and RUNX1 (AML1)
Accounts for 25% B-ALL in children, not affect infants

**Morphology:** Typical lymphoblast morphology

**Phenotype:** CD10+, CD19+, CD34+, CD9-, CD20-, CD66c-

**Genetics:** ETV6 and RUNX1 fusion protein has a dominant negative effect on normal function of RUNX1 (a transcription factor)

The translocation is cryptic on chromosome analysis. Can be detected by FISH

**Prognosis:** Favorable prognosis

**B-lymphoblastic leukemia/lymphoma with t(1;19) TCF3-PBX1**
B-ALL with translocation involving TCR3 (E2A) and PBX1
Accounts for 6% B-ALL in children, less common in adults

**Morphology:** Typical lymphoblast morphology

**Phenotype:** Pre B type (CD10+, CD19+, CD34-, CD9+ strong)

**Genetics:** TCF3 and PBX1 fusion protein is oncogenic and disrupts the normal function of these 2 proteins

**Prognosis:** Unfavorable if CNS is involved

**B-lymphoblastic leukemia/lymphoma with hyperdiploidy**
B-ALL blasts contain >50 chromosomes (usually >66), no translocations or other structural changes

Accounts for 25% B-ALL in children, not affect infants, uncommon in adults

**Morphology:** Typical lymphoblast morphology

**Phenotype:** CD10+, CD19+, CD34+, CD45-

**Genetics:** Numerical increase of chromosomes, most commonly 4, 14, 21, X

**Prognosis:** Favorable prognosis

**T-lymphoblastic leukemia/lymphoma**
Discussed in lesson 9

**Pediatric follicular lymphoma**
A type of follicular lymphoma primarily affecting children and young adults, with high grade morphology and indolent clinical behavior. Aka Pediatric-type follicular lymphoma

Median age of onset 15-18 years, rarely affects adults >40 years
Male predominance: male:female >10:1
Most patients presented with asymptomatic, isolated peripheral lymphadenopathy, commonly at head and neck region, without systemic involvement

**Morphology:** Expanded follicles with serpiginous pattern, tingible body macrophages present
Monotonous, intermediate-sized centroblasts with blastoid appearance, inconspicuous nucleoli. Grading is not recommended

**Phenotype:** Monoclonal B-cell phenotype, CD10+, BCL-6+, BCL-2-, IRF4/MUM-1-

**Genetics:** t(14;18) negative

**Prognosis:** Excellent prognosis, responds to surgical excision
List of slides

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