**Typical first presenting cytopenia**

**Macrocytosis**

**Thrombocytopenia**

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|  | **FA** | **TBD** | **CAMT** | **TAR** |
| **Median age at dx:** | **6.5 y (0-49 y)** | **14 y (0-75 y)** | **0.1 y (0-11 y)** | **0 y (0-0.6y)** |
| **Clinical features** | **- Cafe au lait spots, hypo/hyperpigmentation**  **- Short stature, thumb/radii anomalies**  **- Renal/GU tract anomalies**  **- Microcephaly**  - VACTERL-H association  \* 1/3 may lack anomalies | **Classic triad:**   * **Nail dystrophy** * **Oral leukoplakia** * **Abnormal skin pigmentation**   \* 75% with 1 of classical triad; 45% with all 3  Others: pulmonary/liver fibrosis, esophageal strictures, early grey hair, developmental delay, microcephaly, short stature | **Usually no physical abnormalities** (bruising, rare cardiac defects, CNS abnormalities) | **Absent radii with**  **thumbs present**  Others: cow’s milk intolerance, limb abnormalities (40%), hip dysplasias, abnormal facies, renal malformations, congenital heart disease |
| **Malignancy** | MDS/AML, SCC of head, neck, vulva | MDS/AML, SCC of head, neck, GI) | MDS/AML | MDS/AML |
| **Lab features** | Thrombocytopenia, +/- macrocytosis or anemia 🡪 pancytopenia | Thrombocytopenia or macrocytosis +/-anemia 🡪 pancytopenia | - Type I: early onset of severe thrombocytopenia, early progression (usually by age 2y) to BM aplasia and pancytopenia.  - Type II: Milder; temporary increase in platelets early in life, with possible later development of pancytopenia (by age 3-6). | Thrombocytopenia at birth  Leukemoid reaction common |
| **Bone marrow findings** | Hypocellular marrow. May have erythroid or multilineage dysplasia | Hypocellular  Evolving dysplasia | Hypo/normocellular, markedly decreased/absent megakaryocytes | Absent or small megas. Other lineages normal. |
| **Screening test** | - Spontaneous and DEB/MMC induced  chromosome breaks  - Elevated Hb F | - Decreased telomere length of lymphocytes  - Elevated Hb F | Bone marrow biopsy | Arm X ray |
| **Genetics** | Mutations in genes involved in DNA repair and maintenance.   * FANC-A, C and G most common. * Autosomal recessive (AR) except for *FANCB* (X-linked) and *FANCR/RAD51 (*AD) | Mutations in genes involved in telomere maintenance.   * Dyskerin: 30% - XLR * TIN2: 10% - AD * TERC: 5% - AD * TERT: 5% - AD or AR (<1%) * NOP10: <1% - AR * NHP2: <1% - AR | MPL mutations (thrombopoietin receptor)  - AR | *RBM8A* mutations (mRNA maturation & processing)  - AR |

**Typical first presenting cytopenia**

**Macrocytosis**

**Anemia**

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|  | **Diamond Blackfan anemia** |
| **Median age at dx:** | 3 months, >98% identified within the first year |
| **Clinical features** | ~50% have 1 congenital anomaly, 25% with >1 anomaly:  Short stature, thumb anomalies, cranio-orofacial (tow colored hair, blue sclerae, glaucoma)  Renal/GU anomalies  Cardiac anomalies |
| **Malignancy** | MDS/AML, GI, sarcomas |
| **Lab features** | * Macrocytic anemia (may be absent during the first yr of life or in patients with IDA / thal!) * ↓ Retic * ↑ eADA – may also be elevated in immune deficiencies, hemolytic anemias, MPN, megaloblastic anemias * ↑ Hb F * Strong expression of i antigen – may also be elevated during early infancy and stress erythropoiesis * ↑ serum EPO |
| **Bone marrow findings** | * **Normocellular for age.** * **Profound erythroid hypoplasia.** Some proerythroblasts are seen, but orthochromic erythroblasts are virtually absent. * Dyserythropoiesis. Ring sideroblasts may be present * Normal myelopoiesis & megakaryopoiesis |
| **Genetics** | **Mutations (AD) at structural ribosomal proteins**: RPS19, RPL5 most common   * ~50% of DBA patients lack identifiable mutations! |

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| **Typical first presenting cytopenia** | **Shwachman-Diamond Syndrome**  **Neutropenia**  **Macrocytosis** | **Severe Congenital Neutropenia** | **GATA2 deficiency** |
| **Median age at dx:** | **1 y (0-41 years)** | **3 y (0-70 years)** | **18 y (0-61 years)** |
| **Clinical features** | * **Exocrine pancreatic insufficiency** * **Skeletal changes**: short stature, metaphyseal dysostosis (bell shaped chest) * **Ichthyosis/eczema** * **Immunodeficiency** is a prominent component | **Typically no physical abnormalities**  **Frequent bacterial infections, invasive fungal infections during early infancy** | * Mycobacterial, fungal, viral infections * Pulmonary dysfunction (PAP) * Hearing loss * GU tract anomalies * HPV related warts * Lymphedema, DVT/PE |
| **Malignancy** | MDS/AML | MDS/AML | MDS/AML |
| **Lab features** | * Low trypsinogen, pancreatic isoamylase * Low fecal elastase * Transaminitis | * Isolated low neutrophil counts (<0.5 x 109/L) lasting >3 mo * Monocytosis, hypereosinophilia | * Monocytopenia * B & NK cell lymphopenia * CD4:8 ratio <1 |
| **BM findings** | No specific BM findings: cellularity varies, left shift or hypoplasia of myeloid lineage in 15-50% patients. | Promyelocyte maturation arrest | * Hypocellular * Megakaryocytic atypia * +/- Fibrosis |
| **Genetics** | Mutation in SBDS gene, which functions in ribosome biogenesis  AR | * ELA2 (ELANE) - AD * CSF3R – AR * HAX1 – AR * G6PC3 – AR * WAS – X linked   Causative gene identified in 2/3 SCN patients | Germline heterozygous GATA2 mutation (AD) |