**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 3Others: 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 birthLeukemoid reaction common  |
| **Bone marrow findings** | Hypocellular marrow. May have erythroid or multilineage dysplasia | HypocellularEvolving dysplasia | Hypo/normocellular, markedly decreased/absent megakaryocytes | Absent or small megas. Other lineages normal. |
| **Screening test**  | - Spontaneous and DEB/MMC inducedchromosome 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 anomaliesCardiac 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
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| **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 biogenesisAR | * 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) |