Bone marrow failure and aplastic anemia

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Definition

Aplastic Anemia

- Definition.
- Presentation.
- Types.
- Causes.

Severe aplastic anemia

- 2 of 3 peripheral blood criteria:
  - ANC < 500/ml
  - Platelets < 20,000/ml
  - Reticulocytes < 1% corrected (ARC < 40,000/ul)
- 1 of 2 bone marrow criteria:
  - < 25% cellularity on biopsy
  - 25 – 50% with < 30% hematopoietic cells

Mechanism

Autoreactive T Lymphocytes

Associations

- Autoimmune Disease
- Other immune Disorders.
  - Eosinophilic fasciitis, hypogammaglobulinemia
- Thymoma
- Large granular lymphocytic leukemia (rare)
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Myelodysplasia (hypoplastic MDS)

Diagnosis

- Bone marrow biopsy
- Cytogenetic studies to rule out MDS.
- Rule out Inherited Bone Marrow Failure Syndromes: Chromosome breakage assessment (blood) with diepoxybutane or mitomycin C to rule out Fanconi anemia. Telomere length studies to rule out Dyskeratosis congenita.
- Assess for Paroxysmal PNH by flow cytometry
- R/O Viral infection assessment by serology or PCR
- Evaluation of renal, hepatic, thyroid function

Therapy options.

Immune suppression

Vs

Stem cell transplant

Paroxysmal Nocturnal Hemoglobinuria

Acquired clonal stem cell disorder resulting from mutations in the PIG-A gene.

PIG-A functions in glycosylphosphatidylinositol (GPI) anchor biosynthesis.

PIG-A functions in glycosylphosphatidylinositol (GPI) anchor biosynthesis.

Leads to hemolysis, hemoglobinuria (classically in AM) and thrombosis (venous mesenteric, measure cause of death)

PNH

Diagnose By Flow cytometry to measure CD55/59.

Obsolete hams test.

PNH may present as aplastic anemia but treatment is different

treatment

- Only curative treatment is BMT.
- Eculizumab

Inherited Bone Marrow Failure Syndromes

Frequently associated with physical abnormalities.

Hematologic findings not usually present at birth.

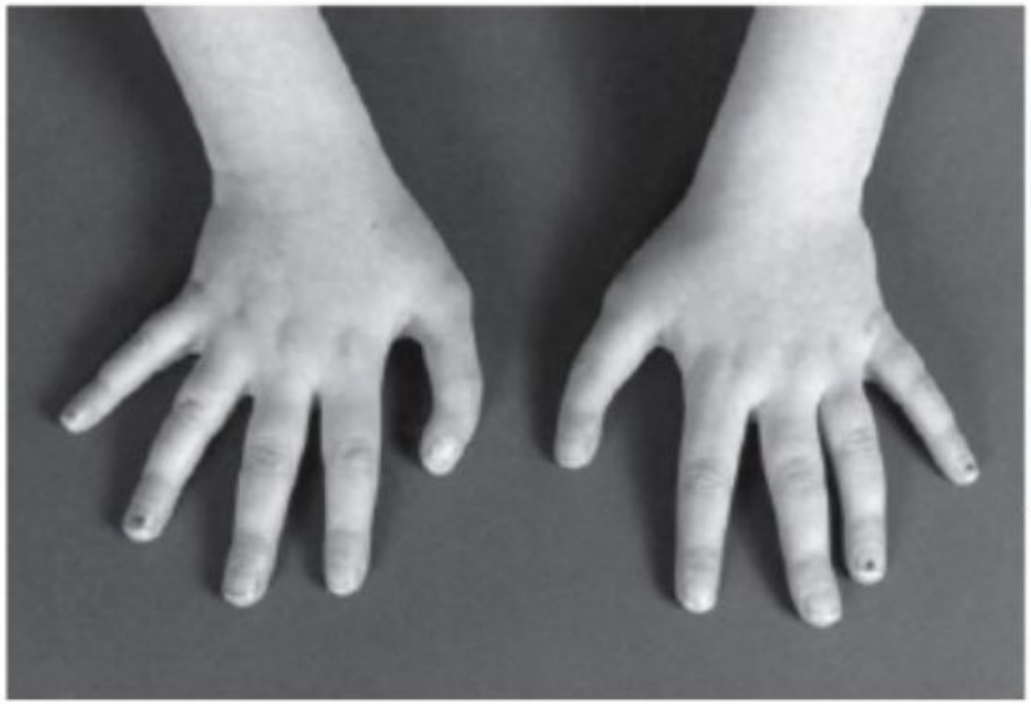
Increased frequency of cancer (malignancy may be the first presenting feature).

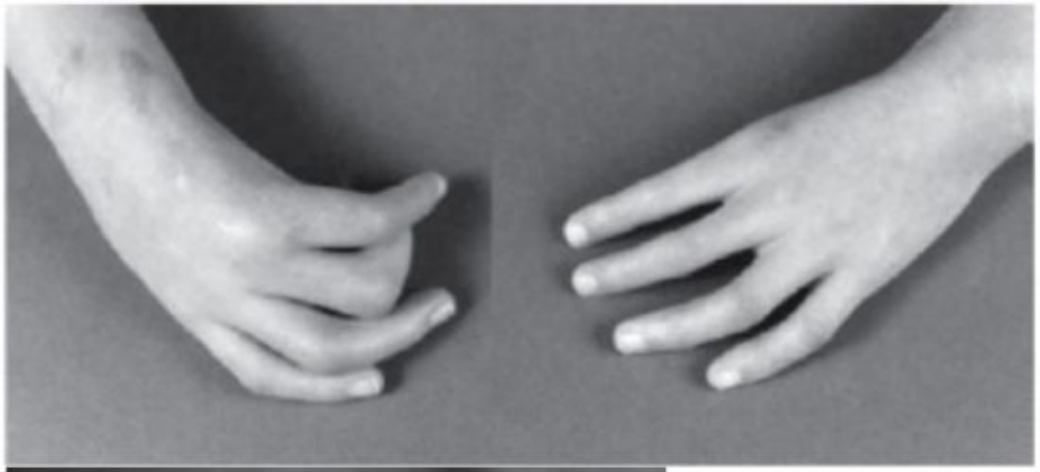
Fanconi anemia

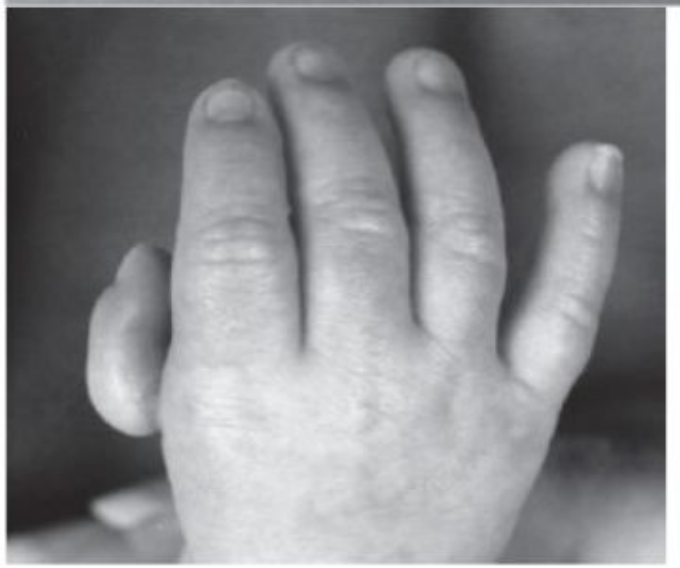
Progressive marrow failure

Congenital anomalies.

Cancer predisposition.

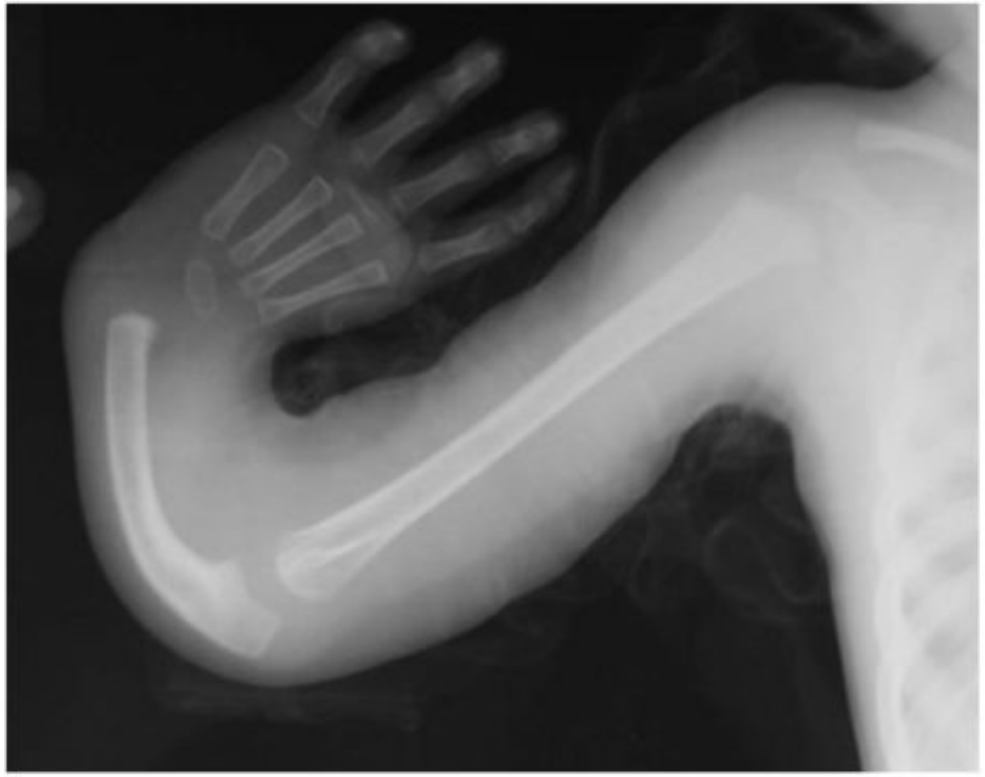


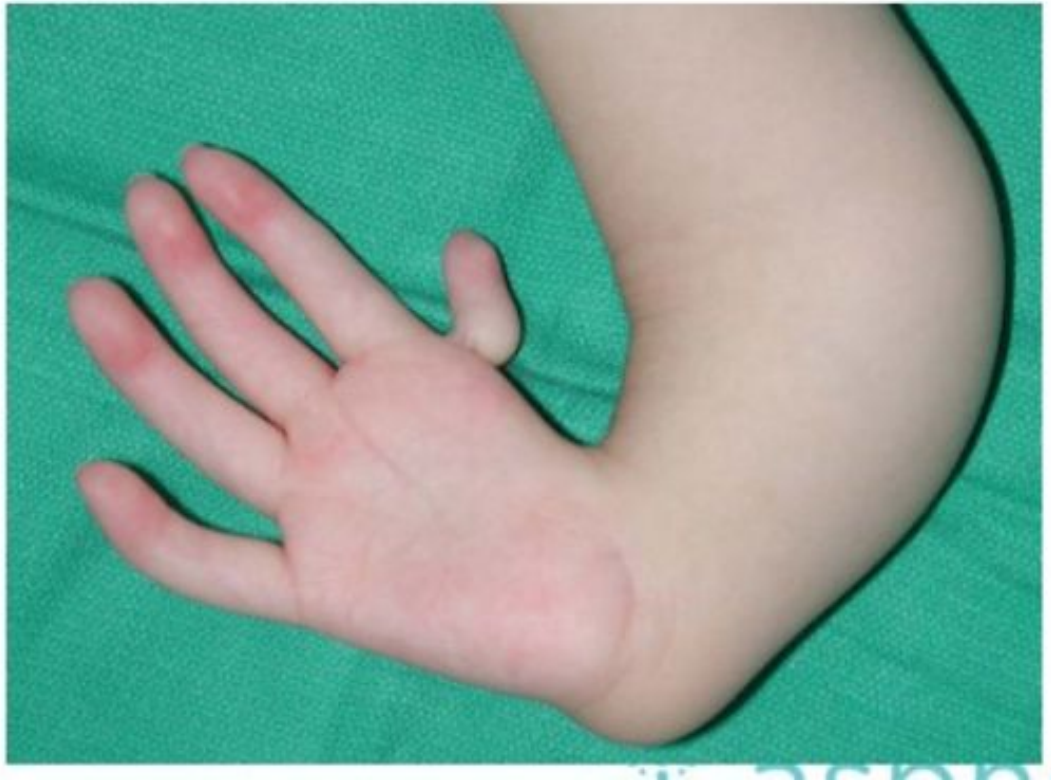




Radial ray anomalies

Kozin and Kiefhaber 2003 Fanconi Anemia Clinical Guidelines, Fanconi Anemia Research Fund, with permission



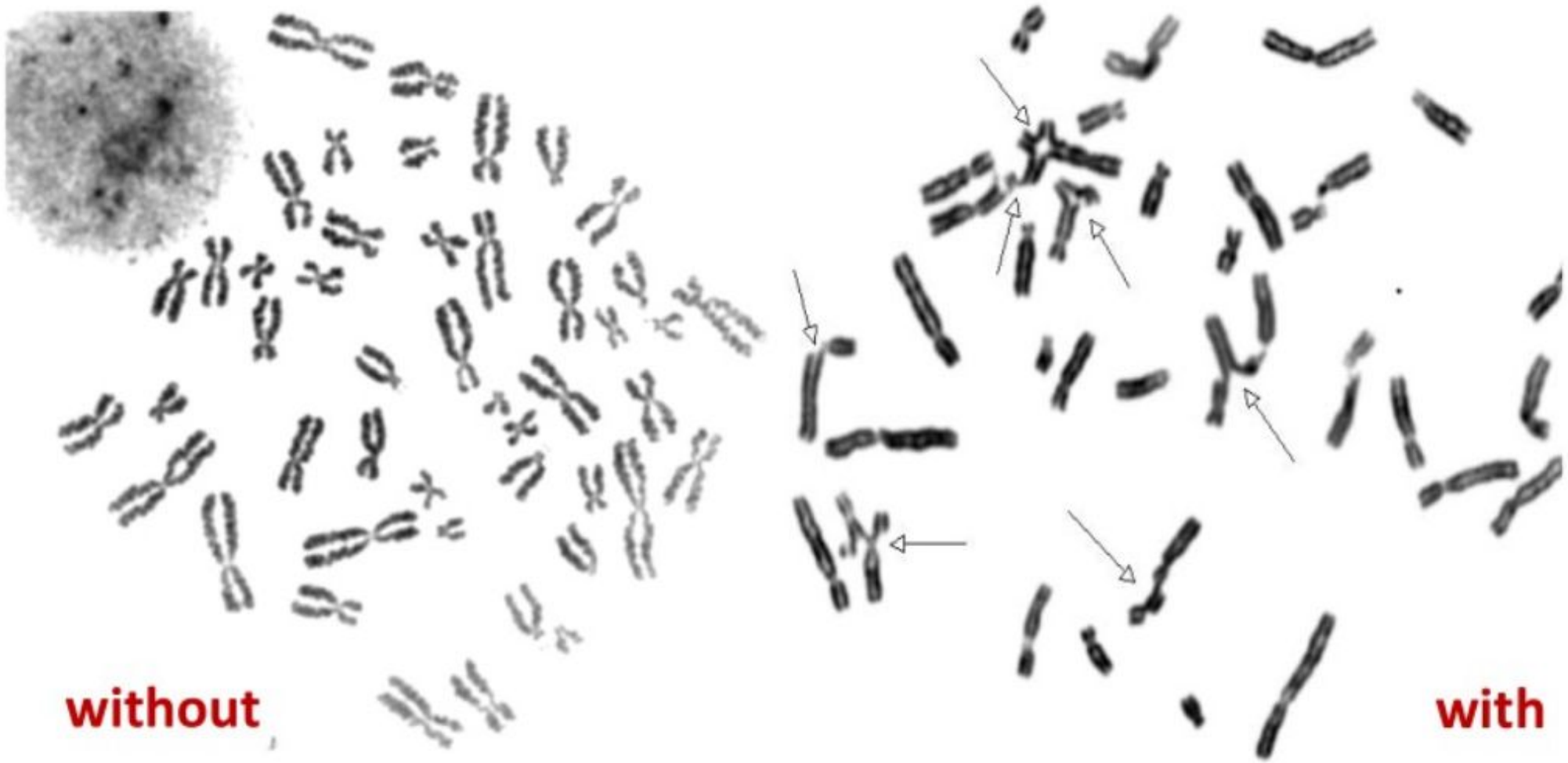


Diagnosis

DNA breakage studies.

Flow cytometry: Clastogen induced G2/M arrest

Mutation analysis: FANC-A, 60-70% of FA, FANC-C, 10-15% of FA.


without
with

Treatment

- Management of congenital anomalies
- Transfusion – fewest units, all irradiated
- Growth factors
- Monitor for development of malignancies (relative risk 1000).
- Androgens.
- HSCT – reduced intensity conditioning

Malignancy in FA

Relative risk 1000.

30% by adult life.

10% Leukemia (AML > ALL) especially M4-M5

10% Solid Tumor: squamous cell head/neck

3% Liver tumor: adenoma and hepatoma

6-8% Female genital tract

Risk increased by HSCT

Malignancy in FA

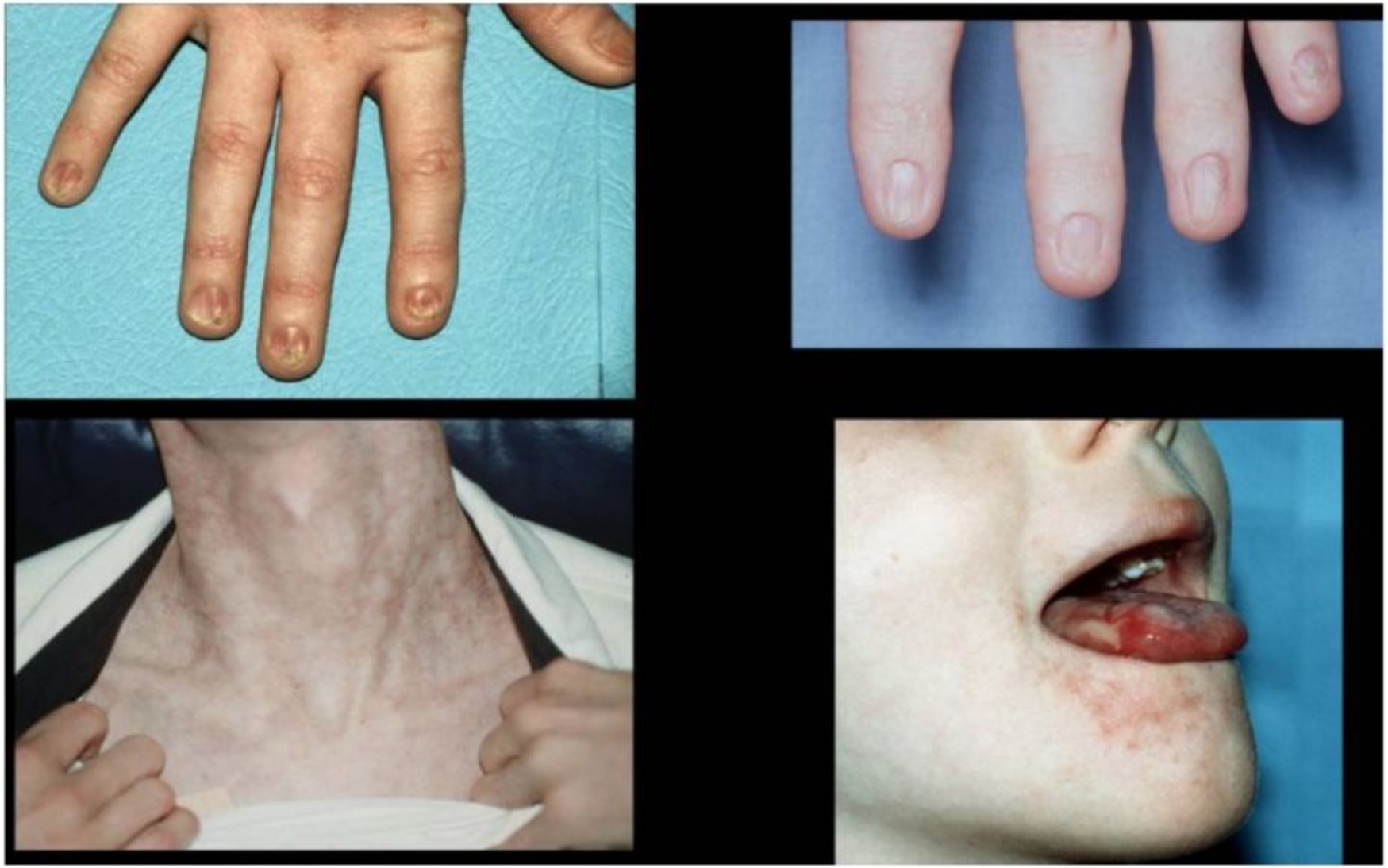
Increased toxicity with chemotherapy.

FA frequently diagnosed after treatment for cancer due to unusual toxicity.

Surgical only approach whenever possible.

Dyskeratosis Congenita

- Ectodermal dysplasia – DNA repair defect.
- Triad – reticulated skin hyperpigmentation, dystrophic nails, mucous membrane leukoplakia – develops with age.
- Aplastic anemia develops in up to 50% in 2nd to 3rd decade.
- Solid organ cancers (head, neck, gastrointestinal) and leukemia at an early age in 3rd to 4th decades, AML.
- Carcinomas of bronchus, tongue, larynx, esophagus, pancreas, skin.



DKC features

- Pulmonary disease
- Dental anomalies
- Esophageal stricture
- Hair loss, early greying
- GI disorders
- Ataxia
- Hypogonadism
- Microcephaly
- Urethral stricture/Phimosis
- Osteoporosis
- Deafness
- Cognitive/developmental delay

DKC

HALLMARK IS VERY SHORT TELOMERES

MULTIPLE MODES ON INHERITANCE.

MOST COMMON MUTATION IS IN THE DKC1 GENE (X-LINKED RECESSIVE).

NOT ALL MUTATIONS IDENTIFIED.

Diagnosis

Clinical features.

Short telomeres.

Mutation analysis.

Treatment

Supportive.

Androgens.

HSCT.

Diamond Blackfan Anemia

- Pure red cell aplasia:
- Macrocytic anemia
- Reticulocytopenia, Paucity of erythroid precursors in marrow
- Congenital anomalies (triphalangeal thumb, short stature, GU, cardiac)
- Elevated Hb F
- Elevated red cell ADA
- Risk for AML/MDS, solid tumors (most common osteosarcoma).

Diamond Blackfan Anemia

- Mutation in ribosomal proteins.
- Autosomal dominant.
- Inherited or sporadic mutation.
- Usually responsive to steroids.
- Some cases are self limited.
- Need to differentiate from TEC (erythrocyte ADA, MCV, HbF, Cong anomalies)
- Refractory cases may need chronic transfusion/ bone marrow transplant.

Pearson Syndrome

- Refractory sideroblastic anemia by 6 months of age
- Exocrine pancreatic dysfunction (fat malabsorption)
- Associated mild neutropenia, thrombocytopenia
- Marrow: vacuolated precursors/ringed sideroblasts
- Death usually as a consequence of acidosis, sepsis, liver or renal failure related to tubular dysfunction
- Median survival-3 years
- Genetics: Mitochondrial DNA deletion so maternal inheritance.

Shwachman-Diamond Syndrome

- Autosomal recessive: 90% with mutation in SBDS gene
- Neutropenia, impaired chemotaxis
- Exocrine pancreatic insufficiency
- Metaphyseal chondrodysplasia, short stature, eczema, cardiac, developmental issues

Management

PANCREATIC ENZYME REPLACEMENT, ADEK SUPPLEMENTS

MANAGEMENT OF CONGENITAL ANOMALIES

G-CSF

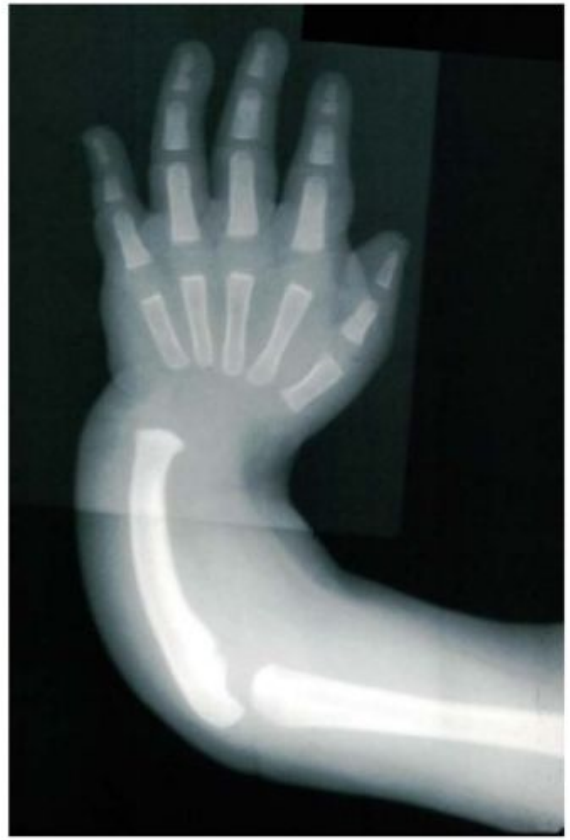
TRANSFUSIONS

MONITORING FOR MDS/AML

STEM CELL TRANSPLANTATION

Amegakaryocytic Thrombocytopenia

- Autosomal recessive : c-MPL gene mutations (thrombopoietin receptor)
- Decreased bone marrow megakaryocytes
- Thrombocytopenia at birth
- Normal platelet size and morphology
- High risk of MDS /AML
- Needs HSCT for cure.



Thrombocytopenia Absent Radius Syndrome

Autosomal Recessive

Thrombocytopenia presenting at birth

Bilateral absence of radii with presence of thumbs (in FA the defect is terminal - thumbs are absent if the radii are absent)

Micrognathia, brachycephaly, hypertelorism, webbed neck, hypogonadism, various lower limb abnormalities 40% , 10% congenital heart disease.

Most outgrow severe thrombocytopenia, eventual platelet count may not be normal

A few words on a totally unrelated topic

Methemoglobinemia