Aplastic Anaemia
Acquired
Hereditary
Acquired Aplasia
Clinical Presentation

- Generally relatively short history of
  - Progressive pallor
  - Bruising, petechiae, epistaxis, gum bleeding
  - Infection

- Clinical findings
  - Pallor, bruising, petechiae, mucosal bleeding
  - Absence of H-S megaly, lymphadenopathy
  - Infection
  - Check for anomalies suggestive of FA
Differential diagnosis

- SAA
- FA
- ALL
- MDS
Initial Investigation

- **History**
  - Drug, toxin exposure
  - Hepatitic illness, including EBV

- **Investigation**
  - FBC & retics
    - Normocytic (macrocytic) aregenerative anaemia
  - LFT’s
  - Viral screening
  - Blood Grp
  - PNH testing
  - DEB/ MMC chromosome breakage test
Diagnostic Investigation

- BMA
- BM trephine biopsy
- BM cytogenetics
  - Clonal abnormality suggests MDS or preleukaemic presentation of ALL
Management - 1

- HLA type family
- Conservative use of blood products
  - Minimise antigen exposure, potential immunisation and transmission CMV/EBV
    - Single donor platelet collections
    - Leukoreduce blood products (filter)
    - Minimise red cell transfusion
- Appropriate antibiotic use
Management - 2

- No Msib donor
  - Immunosuppressive therapy
    - ATG, CSA
  - Unrelated donor search
- Matched Sib
  - BMT 86% 5yr S
  - IS therapy 78% 5yr S
Fanconi Anaemia

- **Commonest hereditary cause** of marrow failure
- **Autosomal recessive inheritance**
  - Prevalence approx 1:100,000 live births
  - Carrier frequency approx 1:300
- **Diverse range of phenotypic expression**
- **Variable time to development of bone marrow failure**
- **Increased risk of development of malignancy**
  - AML, MDS, ALL
  - Squamous cell carcinomas
Physical Findings

- Short Stature 60%
- Cafe- au lait spots, hyperpigmentation 65%
- Radial ray anomalies 54%
- Lower limb –CDH, syndactyly 10%
- Microcephaly 46%
- Microphthalmia, squint, hypertelorism 37%
- Ear anomalies, deafness 31%
- Cardiac / GI anomalies 10%
- Renal, urinary tract anomalies 25%
- Genital anomalies 40%
Diagnosis

- Increased spontaneous chromosome aberrations
  - Breaks, gaps, rearrangements, radial figures
- Markedly increased frequency of chromosome aberrations when cells co-cultured with DNA cross linking agents (MMC, DEB)
  - Considerable variation in response between patients
  - Occasional patients with two cell populations, one N, one with breaks typical of FA (mosaicism)
Biologic Characteristics

- Clinical variability
  - Suggests genetic heterogeneity
- Complementation studies
  - 8 Complementation groups identified (A-G)
  - 7 genes identified to date
    - FANCA, C, D2, E, F, G
    - FANC B, D1 identified as likely representing 2 different allelic mutations of BRCA 2
    - 66% pts FANCA – milder phenotype (most European & North Americans)
    - 12% FANCC - (Predominant mutation in Ashkenazi Jewish population in FANCC)
    - 12% FANC E,
    - Others rare (B 4%)
Genetics

- Gene Identification
  - 1992 FANC-C gene cloned: ch 9q22.3
  - FANC-A 16q24.3
  - FANC-D2 3p25.3
  - FANC-E 6p21-22
  - FANC B, D1 13q12-13
  - FANC F 11p15
  - FANC G 9p13

- Prenatal diagnosis
  - PGD, CVS, Amniocentesis
Gene interaction in FA
Clinical Presentation

- Congenital OR Haematologic abnormalities 44%
- Haematologic and congenital abnormalities 51%
- No abnormality 5%
- Abnormalities > males than females
  - Earlier age onset haematologic abnormalities in males
- Overlapping anomalies in FA pts and non FA pts
- Age of onset of haematologic manifestations highly heritable
Clinical Presentation

- Bone Marrow Failure
  - Gradual Onset (Median M 6.0Y, F 7.5Y)
    - Macrocytosis
    - Thrombocytopenia
    - Anaemia
    - Leukopenia, neutropenia

- Malignancy
  - MDS (5%), AML (10%)
  - SCC (Generally >13yrs, Ave 23yrs)
Therapy

- Management of congenital malformations
  - Surgery
    - Thumbs
    - TOF, other GI
    - Cardiac
    - Anogenital
  - Short Stature
    - Growth hormone
Therapy-2

- Marrow failure
  - Supportive
    - Androgens, GCSF, transfusions, antibiotics
  - Curative
    - BMT
      - Msib, Unrelated

- Malignancy
  - Reduced tolerance of cytotoxics
  - Marked radiation sensitivity
  - Surveillance, early detection, surgery