AN OLDER BOY WITH PANCYTOPENIA

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CASE HISTORY

- 7 year old ,only son of 2^{nd} degree consanguinous parents
- Fever, Reduced activity - 5 days
- Referred for gross pallor noticed by the treating physician

CASE HISTORY

- No significant illness in the past
- No overt bleeds
- Not transfused earlier
- Developmentally normal
- Attends normal school

CLINICAL FINDINGS

- Fairly nourished boy
- Short stature (ht< 3rd centile on IAP chart)
- Gross pallor
- No scleral icterus
- No significant adenopathy
- No Organomegaly
- No cutaneous /mucosal bleeds

OTHER FINDINGS

- Multiple café au lait spots
- Absent right radial pulse
- Proximally placed right thumb
- Hypoplastic right thenar eminence

LAB WORKUP

- Hb-3 g/dl, TC -3300 , platelet-10,000
- Peripheral smear- macrocytic RBC ,severe thrombocytopenia
- Normal coagulation profile
- Normal Ferritin

FURTHER WORKUP

- USG abdomen –renomegaly, hepatomegaly

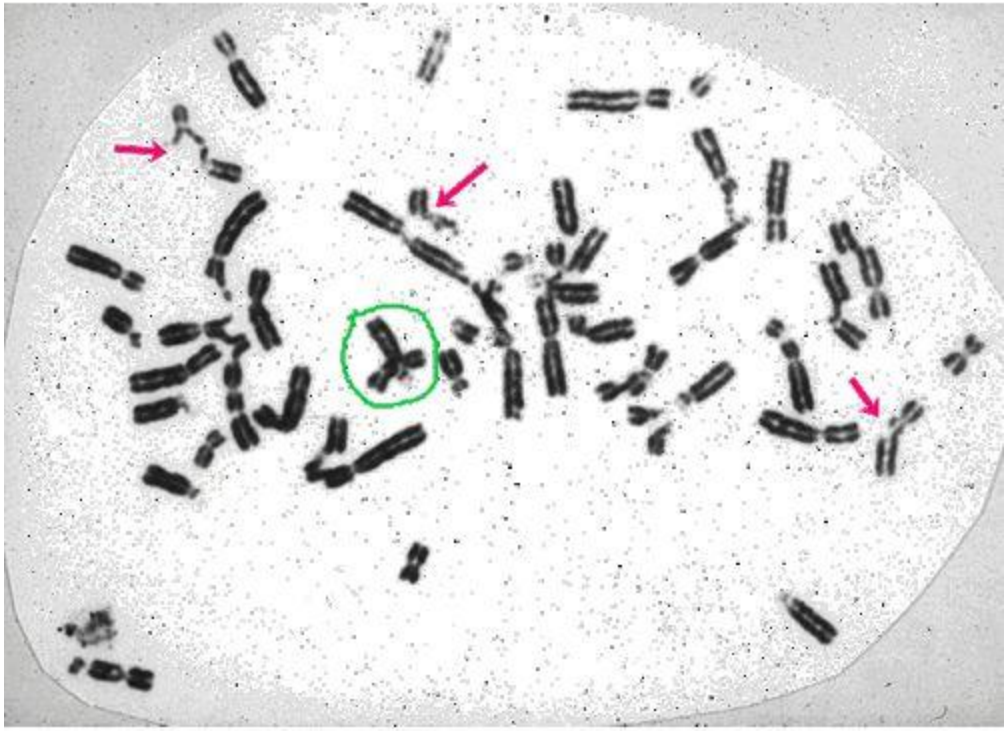
- BMA-

  Markedly hypocellular marrow, with markedly decreased trilineage hematopoiesis, consistent with aplastic anemia

FINAL DIAGNOSIS

- Bone Marrow Failure Syndrome –Fanconi's Anemia

- Classical Chromosomal breakage in Mitomycin induced karyotyping



FA cells were treated with mitomycin C and harvested in metaphase. Typical abnormalities include radial formation (green circle) and chromosome breaks (red arrows).

MANAGEMENT

- Treated with packed red cells,platelet concentrates
- Oral Folic acid and oxymethalone
- Parents counselled about nature of disease,option of BMT & prognosis of the disease

FANCONI ANEMIA

- AR bone marrow failure syndrome associated with multiple congenital anomalies
- Median age of presentation -7 years
- Hematologic dysfunction presents with macrocytosis, thrombocytopenia, leading to progressive pancytopenia and severe aplastic anemia

Frequency of abnormalities in FA

Abnormality	Frequency (%)
Skeletal (radial ray, hip, vertebral scoliosis, rib)	71
Skin pigmentation (café au lait, hyper- and hypopigmentation)	64
Short stature (median height 5th %ile)	63
Eyes (microphthalmia)	38
Renal and urinary tract	34
Male genitalia	20
Mental retardation	16
Gastrointestinal (eg, anorectal, duodenal atresia)	14
Cardiac abnormalities	13
Hearing	11
Central nervous system (eg, hydrocephalus, septum pellucidum)	8
No abnormalities	30

Tischkowitz, M D et al. J Med Genet 2003;40:1-10 (taken from Dokal, 2000)

FA COMPLEMENTATION GROUPS AND FA GENES

FA complementation group	FA gene	Approx. frequency in FA patients (%)	Chromosomal Location
A	FANCA	60	16q24.3
B	FANCB	Rare	Xp22.31
C	FANCC	15	9q22.3
D1	BRCA2	5	13q12.3
D2	FANCD2	5	3p25.3
E	FANCE	Rare	6p21.3
F	FANCF	Rare	11p15
G	FANCG	10	9p13
I	Unknown	Rare	Unknown
J	BRIP1	Rare	17q23.2
L	FANCL	Rare	2p16
M	FANCM	Rare	14q21.2

from Kennedy and D'Andrea, Genes & Development, 2005

PATHOGENESIS

- FA cells are hypersensitive to chromosomal breaks induced by DNA cross linking agents (mitomycin c, diepoxybutane)

- BMA-hypocellularity and fatty replacement

INITIAL MANAGEMENT

- Refer for genetic counseling
  - Testing of siblings
- Renal ultrasound, hearing test, eye exam
- Endocrine evaluation if evidence of growth failure (check growth hormone levels, TSH)
- Referral to hand surgeon for radial ray defects
- Bone marrow biopsy

MANAGEMENT

- Bone marrow failure
  - Transfusions
  - Androgens (e.g. oral oxymethalone) – can improve blood counts in 50% of pts.
    - Side effects: Masculinization, acne, hyperactivity, premature closure of epiphyses, liver toxicity, hepatic adenomas
  - Growth factors (G-CSF, CM-CSF) – should not be used in patients with clonal cytogenetic abnormalities
  - Bone marrow transplantation

MANAGEMENT - GENE THERAPY

- Goal is to permanently correct hematological manifestations by transducing hematopoietic progenitor cells with a vector containing the deficient gene

CARRY HOME MESSAGE

- Importance of thorough physical examination
- Beware of varied presentations of Fanconi's Anemia
- Importance of regular followup and monitoring of side effects

THANK YOU