Inherited Causes of Aplastic Anemia and Myelodysplastic Syndromes

Dr. Yigal Dror

Associate Professor
Marrow Failure & Myelodysplasia Program,
Cell Biology Program, Research Institute
Hospital for Sick Children &
The University of Toronto, Toronto
Topics for Discussion

• Genetic causes of aplastic anemia
• Medical problems
  - Blood
  - Non-blood related
• Genetic aspects
• How is the bone marrow get damaged?
• Diagnosis
• Principles of treatment
Inherited Bone Marrow Failure Syndromes

Production

Low blood counts

Inherited Mutation in a gene

Inherited Bone Marrow Failure Syndromes

Solid tumors

MDS

Leukemia

Leukemia

Inherited Mutation in a gene
IMFSs - General Classification

- Neutropenia
- Anemia
- Thrombocytopenia
- Aplastic anemia
IMFSs - General Classification

**Neutropenia**
- Kostmann
- Cyclic
- Barth
- GSD 1b

**Anemia**
- Diamond Blackfan
- Congenital dyserythropoietic
- Inherited sideroblastic

**Thrombocytopenia**
- TAR
- Familial, AD
- MYH9 – related
- FT/AML

**Dyskeratosis cong.**

**Fanconi**

**SDS**

**Pearson**

**CAMT**
General Characteristics

• **Bone marrow dysfunction**
  – Low blood counts, MDS, leukemia

• **Non hematological manifestations**
  – **Skeletal** (e.g. FA, SDS, DBA, TAR)
  – **Kidneys** (e.g. FA, DBA, TAR)
  – **Cardiac** (e.g. FA, DBA, TAR)
  – **Pancreatic dysfunction** (e.g. SDS)
  – **Skin** pigmentation (e.g. FA, TAR)
  – **Nail anomalies** (e.g. DC)
  – **Solid tumors** (e.g. FA, DC)
  – **No extra-hematological changes**
Case Presentation (1)

• 16 y girl was referred to the Marrow Failure & Myelodysplasia Clinic

• Family had just come to Canada from another country

• Age of 12 years:
  – Bruises
  – Weakness
  – Fever
Case Presentation

Laboratory Investigation

• Hemoglobin 6.5 (normal 12-14)

• Neutrophils 0.48 (normal 1.5-4.5)

• Platelets 12 (normal 150-450)
Case Presentation
Bone Marrow Aspiration & Biopsy

- Reduced bone marrow cells (20%)

- No evidence of preleukemia or leukemia
  - No abnormal cells
  - Normal chromosomes
Case Presentation

• Diagnosed with acquired severe aplastic anemia

• Treated with ATG/CSA/Pred
  → No response
Case Presentation

• Age 14 years
  – Patient was noticed to have short stature and skin pigmentation
  – An inherited bone marrow failure syndrome was suspected
Case Presentation

• chromosomal fragility test

→ Chromosome breaks

Grover, COH 2003
Case Presentation

• Revised Diagnosis

→ Fanconi Anemia
Inherited Marrow Failure Syndromes - Relative Prevalence on CIMFR Data

Disorders

UC
DBA
FA
SDS
KN
FNST
DKC
CN
GSD-1b
Barth
ISA
TAR
CAMT
Reticular D
CDA
Other syndromes with cytopenia

No. of patients

Can cause aplastic anemia
Causes and Course of the Disease

Aplastic Anemia

- Idiopathic: 70%
- Inherited: 25%
- Acquired: 52.5%

No response

Response
Case Presentation (2)

• **42 year old man** presented to a family doctor with increasing pallor and weakness for several months.

• **Family history**
  – Unremarkable. Parents, 2 siblings and 2 children are healthy.
Case Presentation
Laboratory Investigation

- Hemoglobin 7.2 (normal 14-16)
- Neutrophils 0.6 (normal 1.5-4.5)
- Platelets 40 (normal 150-450)
- Smear: blasts
Case Presentation

Bone marrow:
- Reduced cell numbers (30%)
- Fibrosis ("scar tissue")
- 6% blasts (Normal < 5%)
- Chromosome abnormalities
  - Loss of one chromosome 3
  - Loss of one chromosome 5
  - Loss of one chromosome 20
  - translocation between chromosome 5 and 7

→ Myelodysplastic syndrome (MDS)
Case Presentation

• **Careful medical history**
  – During childhood the patient had **pancreatic insufficiency** and chronic marrow failure
  – Was diagnosed with Shwachman-Diamond syndrome
  – Was well without treatment and no follow-up after childhood
Case Presentation

Diagnosis – MDS

Type:
- Syndrome related MDS (SDS) /
- Refractory cytopenia with excess blasts /
- Complex cytogenetic abnormalities
Inherited Marrow Failure Syndromes Causing MDS - Relative Prevalence on CIMFR Data

Prevalence of CMCA/MDS/Leukemia: 35 of 237 patients (15%)

Segbefia et al, In Preparation
Age of Presentation of the Inherited Marrow Failure Syndromes

Diagnostic curves showing age of presentation.
Incidence of the Inherited Marrow Failure Syndromes

- About 40% of the aplastic anemias in children are genetic
  
  \[ \approx 1.5 \text{ per } 10^6 \text{ per year} \]

- Inherited marrow failure syndromes with single cytopenia (one affected cell lineage)
  
  \[ \approx 1 \text{ per } 10^6 \text{ per year} \]

Total

\[ \approx 2.5 \text{ per } 10^6 \text{ per year} \]
How Do We Make A Diagnosis of an Inherited Marrow Failure Syndrome?

• Establishing a diagnosis of bone marrow failure
  – Medical history
  – Family history
  – Physical examination
  – blood counts
  – Bone marrow

• Additional information for establishing a genetic diagnosis
  – Laboratory testing (e.g. adenosine deaminase, chromosomal fragility, telomere length, pancreatic enzymes)
  – Genetic work-up (e.g. for FA, SDS)
Diagnostic Clues

Aplastic anemia

- Fanconi Anemia
- Dyskeratosis Congenita
- Shwachman-Diamond
IMFS Genes and Their Postulated Functions

Cytoplasm

- Enzymes
  - ELA2

- Growth factor receptors
  - cMPL

Cell Survival
- HAX1

Protein Synthesis
- RPS19, SBDS

Nucleus

- Repair of DNA Damage
  - FANCA, B, C, D1, D2, E, F, G, J, L

- Transcription of genes
  - GATA1, CBFA2, HOXA11, GFI1

- Maintenance of the chromosome ends
  - TERC, DKC1, TERT, TIN2, NOP10
Which Patient with Inherited Marrow Failure Needs Treatment and When?

- Severely low blood counts?
- MDS with excess blasts?
  - Leukemia?
  - Solid tumor?

Treatment
Yes
No
Surveillance
Surveillance And Follow-Up - FA, SDS, KN, DKC

- **Periodic follow-up**
  - Taking medical history and physical examination every 6m
  - Blood counts every 3m
  - Bone marrow testing every 1-2 years

- **Indication for treatment:**
  - platelets < 20-30,000
  - neutrophils < 0.5
  - hemoglobin < 7-8
  - MDS with excess blasts or leukemia
  - Solid tumors
<table>
<thead>
<tr>
<th></th>
<th>Blood replacement</th>
<th>Marrow stimulators</th>
<th>Marrow Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>Rbc, Plat</td>
<td>Oxy, GFs</td>
<td>BMT</td>
</tr>
<tr>
<td>DKC</td>
<td>Rbc, Plat</td>
<td>Oxy, GFs</td>
<td>BMT</td>
</tr>
<tr>
<td>SDS</td>
<td>Rbc, Plat</td>
<td>Oxy, GFs</td>
<td>BMT</td>
</tr>
<tr>
<td>DBA</td>
<td>Rbc</td>
<td>Pred, CSA, MCP</td>
<td>BMT</td>
</tr>
<tr>
<td>KN</td>
<td>-</td>
<td>G-CSF</td>
<td>BMT</td>
</tr>
</tbody>
</table>
Supportive Care

- Antibiotics
- Transfusions
- Tranexamic acid
- Growth factors
- Preparation for dental and surgical procedures
- Some restrictions on physical activities, drugs etc. depending on the condition
Summary

• A significant number of the patients with severe aplastic anemia might have inherited diseases (40%?)
• A significant number of the children with MDS might have an inherited marrow failure syndrome (40%?)
• There are many disorders of inherited marrow failure syndrome with significant similarities
• Careful follow-up is important to detect complication at an early stage
• Treatment include transfusions, bone marrow stimulants or bone marrow transplantation.
Acknowledgement

- The patients in our Marrow Failure and Myelodysplasia Program (MFMP)
- The MFMP team (Ms. Pat Canning, Dr. Isaac Odame, Diana Cottingham, Carla Seabrook)
- BMT and leukemia/lymphoma Sections, HSC
- CIMFR co-investigators
- Research Laboratory (Chris Allen, Sally-Lin Adams, Hanming Wang, Trainees)
- Support Groups (FA Canada, SDS Canada, Neutropenia Association Inc., Barth Association, AAMAC)