BONE MARROW FAILURE SYNDROMES

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INTRODUCTION

Bone marrow failure syndromes (BMFS) may involve one or more cell lines and may be inherited/congenital or acquired.

Classification of the BMFS is based on the two parameters above.

Aplastic anaemia (AA) is the prototype BMFS.

AA first recognised by Erlich in 1888. The name AA was coined by a French haematologist – Chauffard in 1904.
# Classification

<table>
<thead>
<tr>
<th>CYTOPENIAS</th>
<th>CONGENITAL OR INHERITED</th>
<th>ACQUIRED</th>
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<tbody>
<tr>
<td>1. Red cells</td>
<td>Diamond Blackfan Anaemia (DFA)</td>
<td>Pure red cell aplasia (PRCA) - 1° or 2°</td>
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<td>2. White cells</td>
<td>Kostmann’s syndrome</td>
<td>Neutropenia or agranulocytosis</td>
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<td>3. Platelets</td>
<td>Amegakaryocytic thrombocytopenia</td>
<td>Thrombocytopenia – 1° or 2°</td>
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<td>Thrombocytopenia with absent radii syndrome</td>
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| 4. Multiple cytopenias | Fanconi’s anaemia  
Dyskeratosis congenita  
Shwachman-Diamond syndrome | Aplastic anaemia – 1° or 2°                               |
**APLASTIC ANAEMIA**

**Definition:** Peripheral pancytopenia (Hb < 10 g/dl; ANC < 1.5 x 10⁹/l; platelets < 100 x 10⁹/l) in the presence of a hypocellular/acellular bone marrow

**Classification:** 1° (idiopathic) or 2° to a number of causes including drugs, toxins, radiation, viruses, autoimmune disease, pregnancy, PNH, malignancy, other (inherited, idiopathic, inevitable, idiosyncratic, infective, immune, industrial, other)

More than 2/3 to 80% have idiopathic aplastic anaemia. Inherited AA is rare in adults.
Incidence: 2/1000 000 per year (higher rates in the Far East – 5-7/1000 000 in China and Thailand), peak frequency in young adults – 20 to 30 years of age, male predominance. A second later age peak may be seen (usually after 60 years)

CHBAH : mean age 26 years, M:F ratio 2.15:1
APLASTIC ANAEMIA

Pathophysiology:
Immune – cytotoxic T cells, produce cytokines, inhibit the differentiation of the HSC progenitors and induce apoptosis (INF induce Fas expression on CD34 cells leading to apoptosis)
Intrinsic defect of the HSC
Abnormalities in the bone marrow microenvironment
Extrinsic damage to the bone marrow
Clinical features:
Symptoms and signs are related to the bone marrow failure – anaemia, thrombocytopenia (bleeding) and leucopenia/neutropenia (infection)
Other clinical features or dysmorphic features suggest an inherited or secondary cause
Investigations:
**FBC- NNA ± macrocytic, moderate-severe balanced pancytopenia, reversal of the neutrophil lymphocyte ratio, reticulocytopenia, and no abnormal cells in the peripheral blood**

**U&E, LFT’S, haematinics, INR/PTT, HIV, Hepatitis studies, CMV, EBV, ANF, flow cytometry for PNH**

**Infection – CXR, blood and urine cultures etc.**

**BMAT – hypocellular/acellular marrow, no morphologic abnormalities, cellularity replaced by fat spaces, exclude secondary cause**

**Relevant tests for inherited causes**
APLASTIC ANAEMIA

NORMAL BONE MARROW BIOPSY

APLASTIC ANAEMIA BONE MARROW BIOPSY
APLASTIC ANAEMIA

Approach to aplastic anaemia:
1. Exclude other causes of pancytopenia
2. Exclude inherited and secondary causes of aplastic/hypoplastic anaemia
3. Assess the severity of the aplastic anaemia
4. Consider the most appropriate treatment option for the individual patient (based on history, examination, investigations – FBC; BMAT; other)
CAUSES OF PANCYTOPENIA

1. PANCYTOPENIA ASSOCIATED WITH A HYPOCELLULAR/ACELLULAR BONE MARROW
   Aplastic Anaemia (Primary – idiopathic and inherited)
   Secondary hypoplastic anaemia due to:
   Drugs – cytotoxics, antibiotics, anticonvulsants, antithyroid agents, etc.
   Viruses – hepatitis virus, CMV, EBV, HIV, Parvovirus B19
   Radiation
   Toxins – Benzene, CCL4, DDT, insecticides, alcohol, etc.
   Autoimmune disease – SLE, eosinophillic fasciitis
   Malignancy – AML, ALL, MDS, carcinoma
   PNH
   Other – pregnancy, thymoma, other infections etc.

2. PANCYTOPENIA ASSOCIATED WITH A HYPERCELLULAR BONE MARROW
   Hypersplenism
   Megaloblastic anaemia
   Myelodysplastic syndrome
   Infections (e.g. HIV, Tuberculosis)
   Other – haemophagocytosis
CAUSES OF PANCYTOPENIA

3. PANCYTOPENIA ASSOCIATED WITH BONE MARROW INFILTRATION
Malignancy – haematological (leukaemias, lymphomas, myeloma etc.) and non-haematological (carcinomas – lung, breast, thyroid, kidney, prostate etc.)
Granulomas (tuberculosis, sarcoidosis, brucellosis)
Fibrosis (primary, secondary)
Other – osteopetrosis etc.
# APLASTIC ANAEMIA

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>CRITERIA</th>
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<td>Severe</td>
<td>BM cellularity &lt;25% (or 25-50%, with &lt;30% of BM cellularity attributed to residual haematopoietic cells) and ≥ 2 (or 2 out of 3) of the following: Peripheral blood neutrophil count &lt; 0.5 x 10⁹/l Peripheral blood platelet count &lt; 20 x 10⁹/l Peripheral blood reticulocyte count &lt; 20 x 10⁹/l (corrected reticulocyte count &lt; 1%)</td>
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<tr>
<td>Very severe</td>
<td>As above, but peripheral blood neutrophil count must be &lt; 0.2 x 10⁹ /l</td>
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<td>Nonsevere</td>
<td>Hypocellular bone marrow with peripheral blood values not meeting criteria for severe or very severe aplastic anaemia. Hypocellular bone marrow with 2 out of 3 of the criteria for pancytopenia</td>
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APLASTIC ANAEMIA

Management:
A. Supportive:
a) Identification, removal and correction of any secondary cause
b) Blood and blood product transfusion
c) Neutropenic measures
d) Measures to curtail mucosal bleeding
e) Other – e.g. Iron chelation
Management:
B. Specific
a) Severe AA – HSCT or combined immunosuppressive therapy (ATG/ALG as the backbone, together with corticosteroids and cyclosporine)
b) Other immunosuppressive drugs – MMF, cyclophosphamide, alemtuzumab etc.
c) Androgens
d) Other
**Prognosis:**
HSCT long term survival rates 70-90%. Transplant related morbidity and mortality higher in adults (higher risk of GVHD and infections). ATG mostly PR and less CR than with HSCT (RR – 60-70%). Relapses may be treated with another course of ATG.

**Complications:**
- Therapy related (androgens, corticosteroids, cyclosporin)
- Progression to more severe disease
- Evolution to PNH (5 -10%)
- Transformation to MDS and acute leukaemia (5-10%)
- Iron overload
FANCONI’S ANAEMIA

Autosomal recessive
Phenotypic or genotypic
Short stature, skeletal abnormalities, skin changes, abnormalities of the genitourinary tract, other
Aetiology – mutations in DNA repair genes
Diagnosis – DEB test
Management – supportive, androgens, HSCT Complications – side effects of treatment, acute leukemia in 10%
FANCONI’S ANAEMIA

X-RAYS SHOWING ABSENT THUMB IN FANCONI’S ANAEMIA

IVP SHOWING LEFT KIDNEY IN PELVIS AND NORMAL RIGHT KIDNEY
BMFS may be inherited or acquired
BMFS may manifest as single or multiple cytopenias
Aplastic anaemia is the prototype BMFS
More than 2/3 to 80% of aplastic anaemia is idiopathic. Inherited AA is rare in adults
Suspect the disease in young patients, with moderately severe, balanced pancytopenia, reticulocytopenia and reversal of the normal neutrophil to lymphocyte ratio
CONCLUSION

Early referral to a specialised centre. Use leucodepleted blood products up front if AA is suspected.

Four step approach to the work up and management of aplastic anaemia.

Management includes supportive care and specific treatment – mainstay of treatment for severe aplastic anaemia involves HSCT or immunosuppressive therapy. HSCT is potentially curative.

Significant challenges in our patients – late referrals, repeated blood transfusions without an attempt to define the cause of the cytopenias, use of non-leucodepleted blood products prior to referral, prolonged use of corticosteroids, high rate of HLA-incompatibility etc.
REFERENCES


THANK YOU