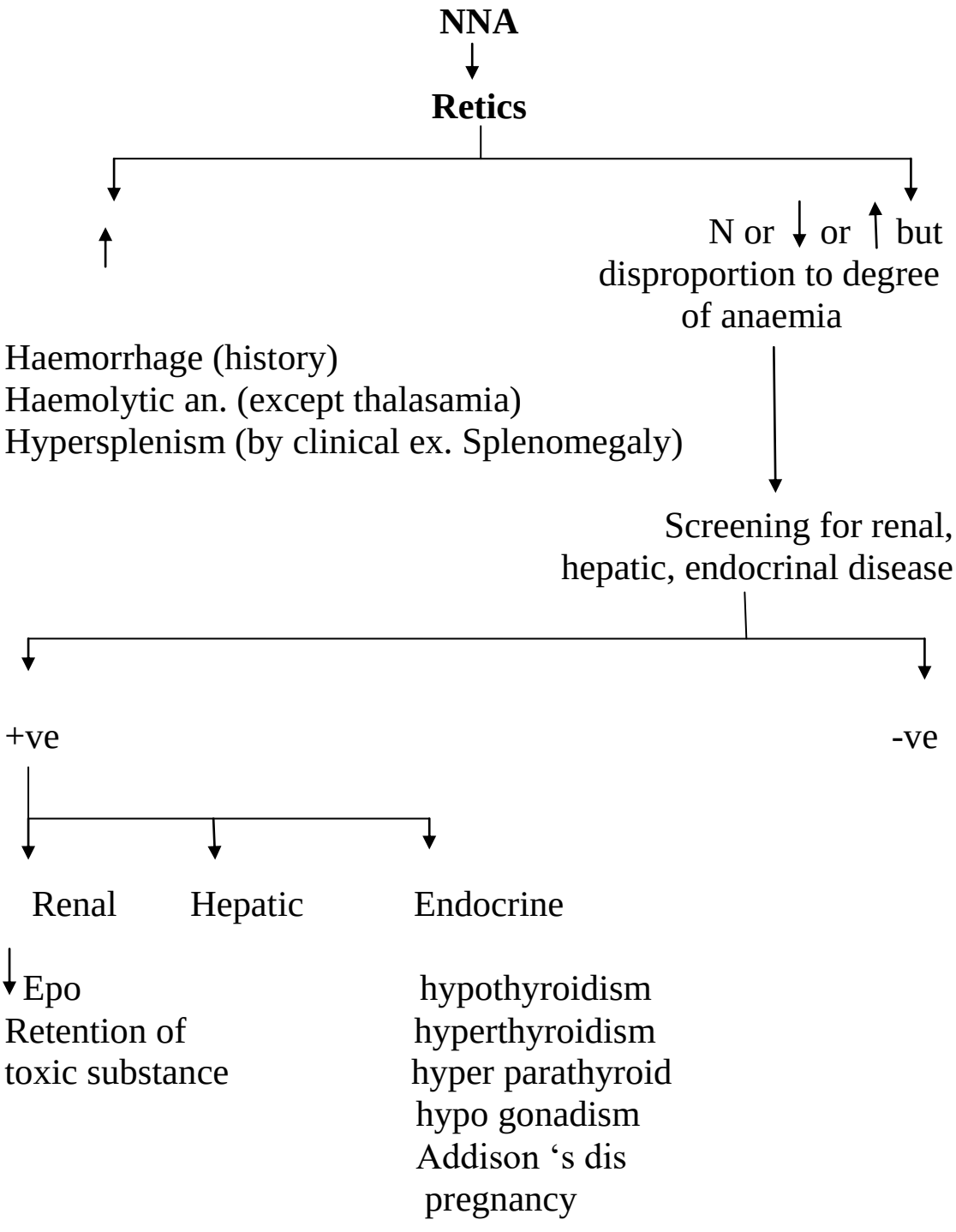
Normocytic Normochromic Anaemia



- ve

↓

serum Iron

N or ↑ → ↓

BMA+ biopsy

↓

Abnormal BM

↓

Aplastic an

Infiltration by leukaemia or fibrous tissue

Pure red cell aplasia

MDS

Cong. Dyserythropoietic an.

low ↓

an. of chronic disease

early Fe def. an.

Bone Marrow Failure
= Ineffective Erythropoiesis
= Normocytic Normochromic Anaemia e' ↓retics

e' Hypocellular BM
Quantitative type

Tri lineage failure
Aplastic

Single lineage failure
Pure red cell aplasia
Neutropenia
Amega karyocytic thrombocytopenia

e' Hypercellular BM
Qualitative type
= Ineffective erythropo.
= Dyserythropoiesis

Aplastic
ch ch by:
-pancytopenia
- hypocellular BM
- no abnormal cells in PB, BM in most cases.

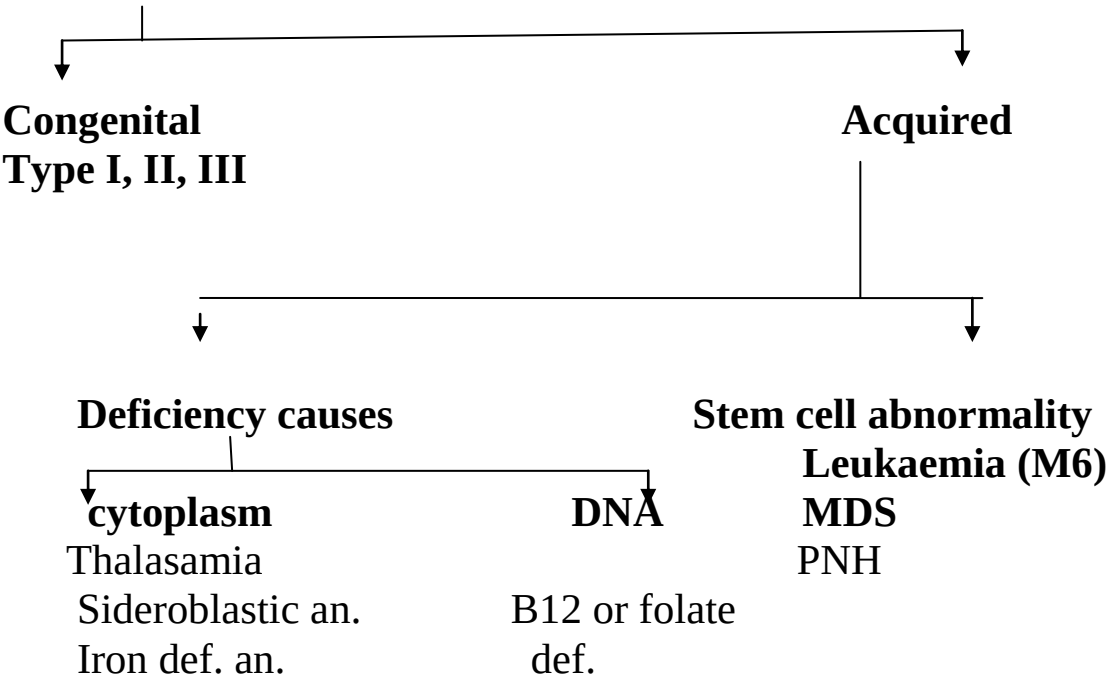
Causes:

1- Stem cell depression:
e.g: Aplastic anaemia

2-Erythropoietic factors:
Epo renal failure
all hormones endocrinal an.

3-HIM:
replacement of haemopoietic environment by:
fibrosis , leukaemia, lymphoma

Dyserythropoiesis

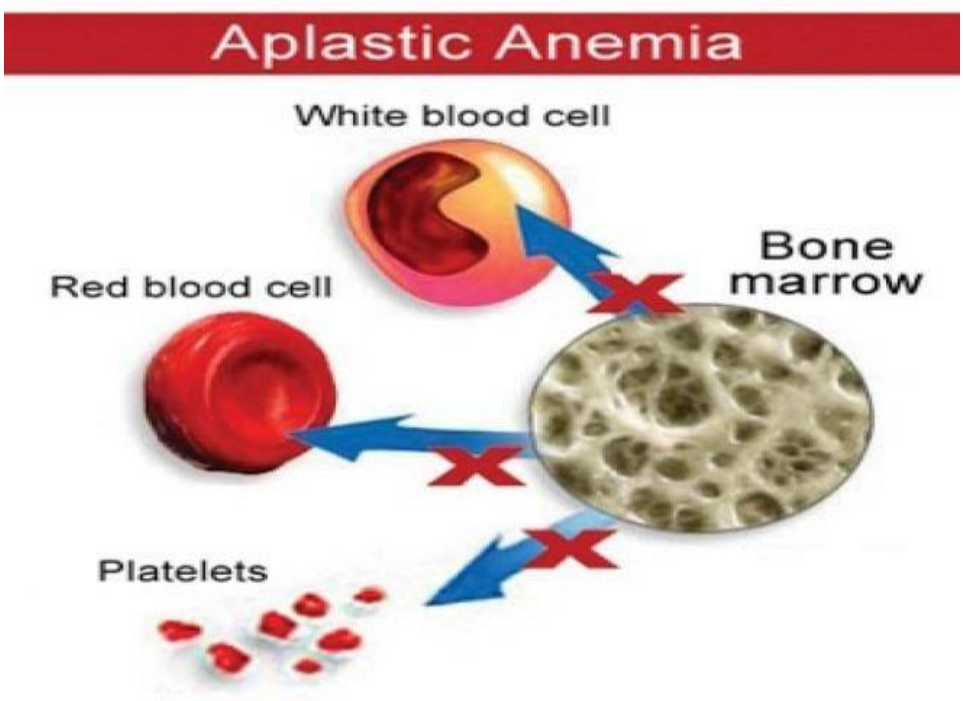


Aplastic Anaemia

Def:

It is a state of BM failure resulting in pancytopenia e' hypocellular marrow.

BM failure: stem cell failure to produce mature cells rather than production of abnormal cells & destruction.



Causes:

It is either, hereditary or acquired, e' or e' out a cause.

BM cellularity may be patchy → so BM biopsy is recommended for diagnosis & for D.D from conditions ch. by infiltration or suppression of BM cells.

Table 1: Causes of aplastic anaemia.

Primary	Secondary
Congenital (Fanconi and non-Fanconi types)	**Ionizing radiation:** Accidental exposure (radiotherapy, radioactive isotopes,nuclear power stations)
Idiopathic **acquired**	**Chemicals:** Benzene, organophosphates and other organic solvents, DDT and other pesticides
	Drugs: Those that regularly cause marrow depression (e.g. busulfan, cyclophosphamide, anthracyclines). Those that occasionally or rarely cause marrow depression (e.g. chloramphenicol, sulphonamides, gold, anti-inflammatory, antithyroid, anticonvulsant/antidepressant drugs)
	Viruses: Viral hepatitis (non-A, non-B, non-C, in most cases), EBV

EBV, Epstein–Barr virus.

BM failure

mechanisms:

- Stem cell disorders
- Abnormal microenvironment
- Impaired production or release of GFs
- Cellular or humoral immune suppression of BM

Classification of A A:

congenital (fanconi an.)
acquired
idiopathic (65% of cases)

Acquired Aplastic Anaemia

Aeitology:

1- Drugs: depends on type, dose, duration

Either do to↑ dose (or ↑duration) or abnormal susceptibility to certain drugs (which normally doesn't cause aplasia in most patient) or through definite mechanisms as:

A-Benzene : → marrow toxins

B- Chloramphenicol: ↓ protein synthesis

C- Streptomycin: ↓ '' ''

D- Actinomycin: ↓ m RNA

Genetic predisposition plays a role

Defects in detoxication or excretion may also play a role (hepatic or renal causes)

2- Radiation:

Single high dose R → chromosomal breaks → rejoined later.

In repeated exposure → rate of breaks is higher than rejoining → chromosomal aberrations → AA

TBI → destroy BM totally

3- Viruses:

Viral hepatitis → pancytopenia after 6-12 ws of onset of disease.

HIV → pancytopenia

EBV → neutropenia or thrombocytopenia

Parvo virus → pure red cell aplasia

4- Pregnancy:

Immune mechanisms

5- Connective tissue disease:

e.g.: SLE, R.A → immune mechanism → abnormal or suppressor cs against haemopoietic progenitor

Pathogenesis:

Stem cell of genetically predisposed individual

↓ accumulation effect of multiple harmful exposures

Polyclonal injury of all stem cells → No replication

Clinical picture:
History of drug intake, irradiation, disease, etc….
Signs & symptoms of pancytopenia:
Insidious onset → pallor, weakness, fatigue
Dramatic onset → fever, chills, pharyngitis
Infections ⟶ due to neutropenia
Bleeding ⟶ due to thrombocytopenia

Table 2: Three 3 patterns are found:

Stable AA or Severe AA	Fluctuating AA	Unstable AA
Bad prognosis criteria: Cellularity < 25 % Cellularity < 50 % + 2 of the following: Neutrophils < 500/ ml Platelets < 20,000 Retics < 1 %	May present as: Small degree of pancytopenia OR deficiency in 1 lineage ↓ May fluctuate over years ↓ Progress to aplasia	Some cases show improvement in peripheral counts which may be associated e' abnormal clone e.g: MDS ,or ALL, or PNH

Lab investigations:
1- CBC:
Pancytopenia
NNA e' some macrocytosis due to ↑ Epo
Retics < 1 % or zero
2- BM aspirate:
Hypocellular BM e' ↑ fat spaces, lymph cs, plasma cs, MQ, mast cs.
The remaining haematopoietic precursors r N in appearance.

Severe AA:
A- cellularity < 25 %
B- cellularity < 50 % + 2 of the following:

neutrophils < 500/ml
platelets < 20,000
corrected retics < 1

$$\frac{\text{Retics X Ht of patient}}{\text{Normal Ht}}$$

If neutrophils < 200/ml **{ very bad prognosis}**

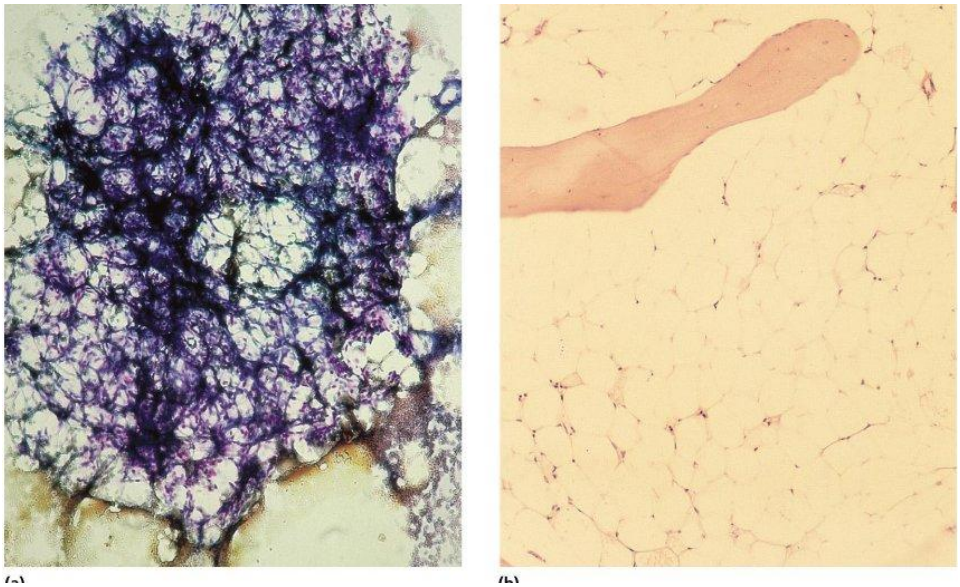


Figure 22.1 Aplastic anaemia: low power views of bone marrow show severe reduction of haemopoietic cells with an increase in fat spaces. **(a)** Aspirated fragment. **(b)** Trephine biopsy.

3- BM biopsy: Is a must
It is done for patchy distribution to exclude other causes of pancytopenia
Important for assessment of severity of AA
Fat replacement e' or e' out remaining islands of cellularity.
Scanty reticulin fibres

4- Ferrokinetics: بطئ

- Prolonged plasma clearance time
- Decreased iron utilization by BM
- Most of iron is taken by liver
- ↓ Entry of radioactivity in circulation after 14 days
- ↓ Red cell iron utilization

5- BM culture:

↓ growth of CFU-MK, BFU-E

6- Serum:

↑ Erythropoietin

↑ Iron

7- MRI:

Estimate BM aplasia & differ it from hypoplastic MDS

8- Chromosmal studies:

Chromatid breaks (imp. Only in Fanconi's an. (cong. AA)

D.D:

- Hypoplastic MDS
- Aplastic ALL
- Hairy cell leukaemia (HCL)
- PNH

Residual cs show:

Morphological, cytochemical, cytogenetic & immunological specificity for each disease.

ttt:

1- Supportive ttt:

Blood products e.g: packed RBCs , platelets

Prophylaxis & ttt of infections e.g: antibiotics

G-CSF, or GM-CSF

2- Restoration of BM activity:

Haemopoietic Growth Factors

Splenectomy (in patients resistant to plat. transfusion)

3- BM transplantation (BMT):

Especially in young pt {ttt of choice}.

II-Hereditary Aplastic Anaemia

1- Fanconi 's anaemia (FA)

Aeitology & pathogenesis:

- AR
- The defect is due to ↑ sensitivity to chromosomal damage by DNA cross linking agents e.g: alkylating agents as cyclophosphamide → ↑chromatid abnormalities indicating a defect in DNA repair.

C/P:

- Low birth weight & delayed growth.
- Microcephaly , small mouth.
- Hypo & hyper pigmentation of skin (cafe' au laut spots).
- Skeletal abnormalities→ short stature.
- Mental retardation.
- Hypo gonadism, undesended testis.
- Renal anomalies e.g: horse shoe or pelvic kidney.
- BM failure at the age of 5-10 years.
- AML is common **{FA is pre leukemic}**

- **Lab investigations:**

CBC:

- Pancytopenia,↓ RBCs, WBCs & platelets, develop gradually.

BM:

- Hypoplasia starts at 5-10 ys.
- High incidence of AML (10%).

Chromosomal studies:

- chromatid breaks or translocations.

Serum:

- ↓ GM CSF ↓ BFU E

D.D:

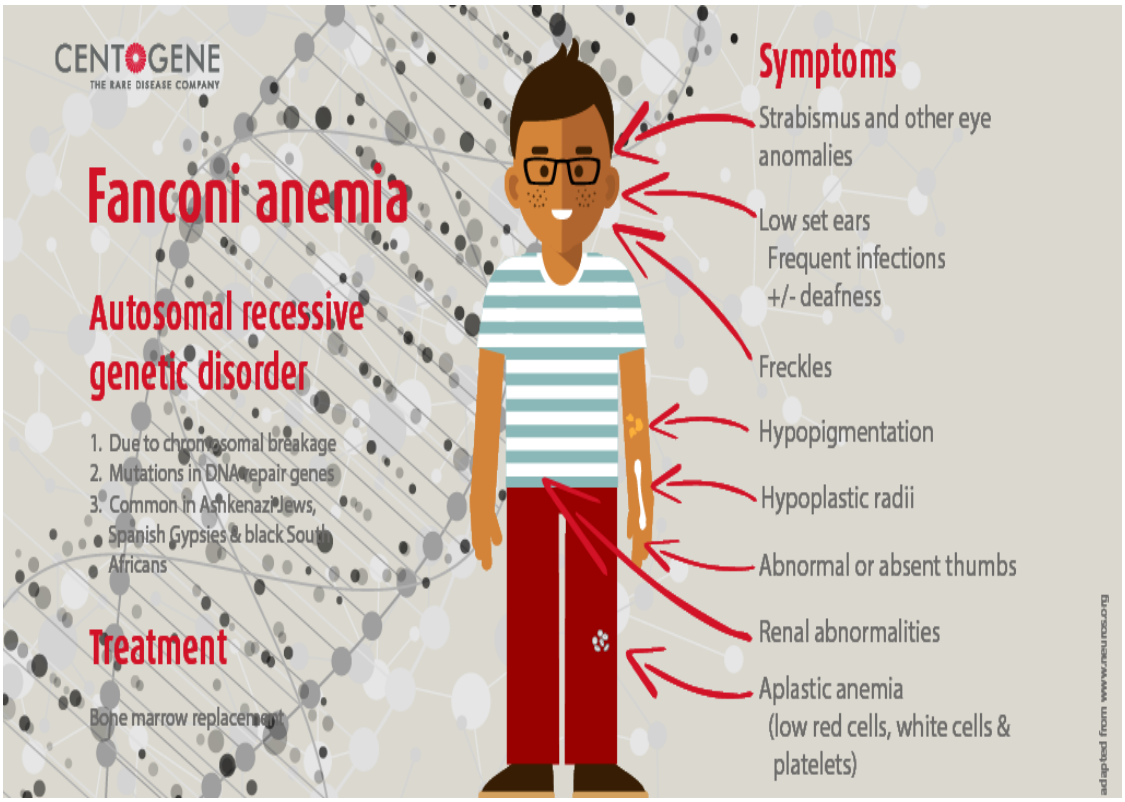
- Other causes of hereditary AA e.g: **Schwachman-Diamond syndrome.**

ttt:

- Responds to androgens.
- BMT (immediately after diagnosis as it may → AML).

Prognosis:

- Rarely patients may enter remission (at puberty due to androgens).
- E' out BMT, patients may die from transformation to AML.



2- Dyskeratosis Congenita

- Chromosomes r N e' no sensitivity to alkylating agents as FA.
- Skin & nail atrophy.
- Progressive BM failure starting at 3^{rd} – 4^{th} decade.
- BMT may be used

D.D: **Schwachman – Diamond Syndrome**

- **AR**
- Pancreatic insufficiency e' neutropenia → hypoplastic BM.

ttt :

BMT.

Single lineage BM Failure

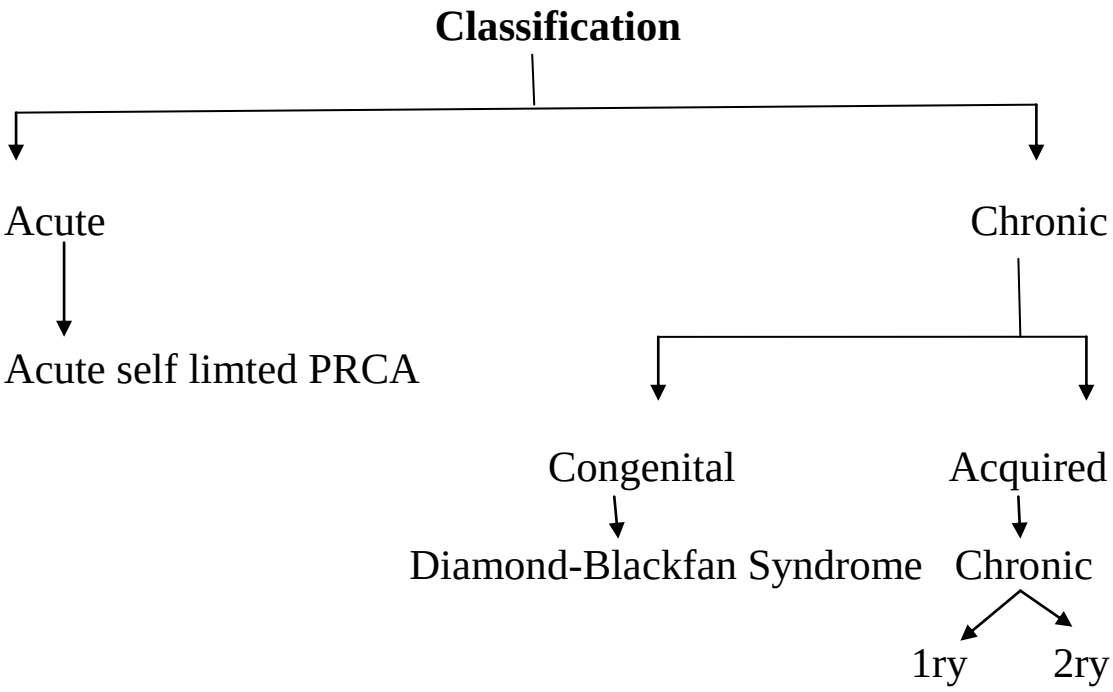
I- Pure red cell aplasia

Def:

Isolated depletion of erythroblasts.

Ch ch:

- Anaemia, ↓retics.
- Absent erythroid series in BM or absent mature series.
- Normal myeloid & megakaryocytic series.



1- Acute self limited PRCA

(acquired, transient)

A- Parvo virus 19 Aplastic crisis

Aeitology:
Parvo virus B19
Pathogenesis:

- The virus is tropic for BFU-E & erythropoiesis stops during acute infections (5-10 days).
- Recovery begins e' the appearance of Ig M Abs to virus.
- E' N RBCs life span ⟶ no anaemia.
- But in H.A. ⟶ fall of Hb occurs.

N.B:
Immuno suppressed or immuno deficient patients, may develop prolonged PRCA.
C/P:

- Progressive pallor.
- Anaemia ⟶ ↑ progression.
- ↓ Retics.
- ↓ Bilirubin

Recovery:

- Associated e' bony pains (due to formation of erythroid cs & gaining of BM function).
- ↑ BM erythroid series.

B- Transient erythroblastopenia of childhood

PRCA due to other viral infection.
Lasts for few weeks .
Recover spontaneously.

2- Chronic Constitutional
= Congenital Pure Red Cell Aplasia
= Diamond-Blackfan Syndrome

Aeitology & pathogenesis:

- Occurs in childhood.
- Unknown mechanisms.
- May be in utero parvo virus infection.
- Inherited defect in BFU-E, CFU-E.
- Micro environment defect hits Epo.
- May be immunological disorder → response to steroids.

C/P:

- Anaemia, starts at birth or 6 month.
- Splenomegaly: may develop in some patients e' prolonged transfusion.
- Dysmorphism: in 50% of patients (cleft palate, flat nasal bridge).

Lab investigations:

CBC:

NNA e'↓ retics.
may be pancytopenia

BM:

- ↓ Erythroid series.
- Normal myeloid & megakaryocytic series.

Hb electrophoresis:

↑ Hb F.

D.D:

- Fanconi anaemia.
- Aplastic anaemia.

ttt:

- Steroids.
- Splenectomy.

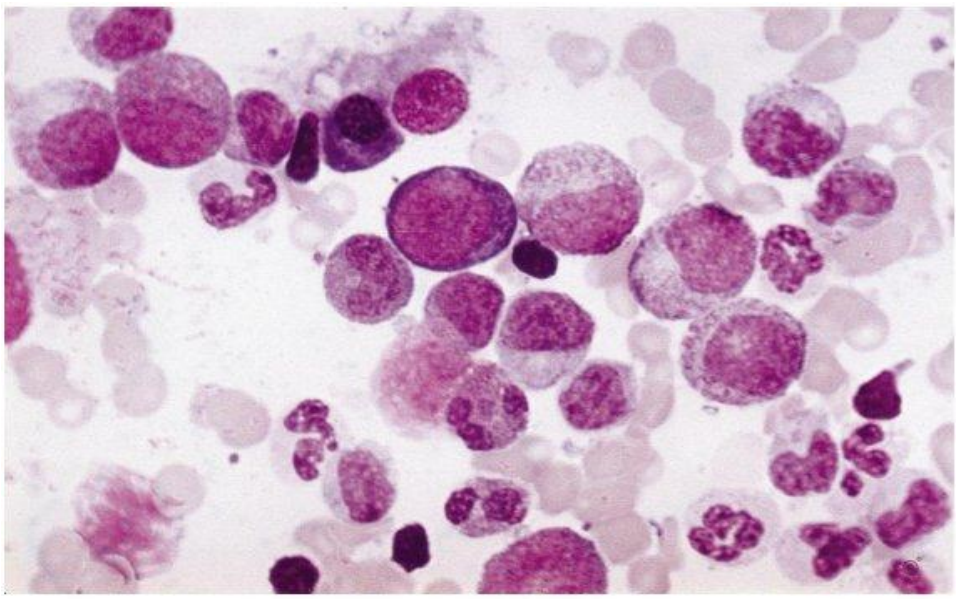


Figure 22.4 The bone marrow in primary red cell aplasia. There is selective loss of erythropoiesis.

3- Chronic Acquired (2ry) PRCA

Occurs in adults.

Causes:

1- Thymoma:

10-20 % of PRCA have thymic tumor.

Diagnosed by CT.

Prognosis:

50% respond to thymectomy.

In non responders → steroids

2- Lymphoma:

B- T cell lymphoma.

3- Autoimmune diseases:

In A gamma globulinaemia & collagen diseases (SLE, R.A), there is Ig G against:

- erythroid progenitor cells.
- Epo
- Epo receptors

4-Drugs:

e.g: Phenytoin, procainamide.

C/P:
Pallor
Thymoma
Lab:
CBC:
NNA , ↓ retics
WBCs & platelets N.
Serum:
↑ serum iron
↑ ferritin (no utilization).

BM:
↓ Erythroid elements.
Serum:
Detection of serum Ab (Ig G).
X- ray:
Anteroir mediastinal mass (thymoma).

Single lineage BMF:

II- Neutropenia associated e' marrow failure
III- A mega karyocytic thrombocytopenia