Microcytic Hypochromic Anaemia

Sideroblastic Anaemia

Transferrin-Iron

↓

BM

85% — Erythroid cs — For Haem synthesis

15% — storage Fe in MQ — Ferritin, Haemosidrin

Sideroblasts	**Siderocytes**
30-40% of marrow normoblasts -Contain cytoplasmic Fe granules -They r considered as stores for Fe to be used for Haem synthesis	Fe granules in RBCs which are removed during passage of RBCs into the spleen (mature RBCs contain 1 or more siderotic granules) **Pappenheim body** Blue e — Perl's stain purple e — conventional stain -Normally it isn't present in P.B -It is present only in Splenectomy or Sideroblastic anaemia

Types of Sideroblasts

Normal	Abnormal Pathological Sideroblasts	
30-40% in BM -Contains 1 or more granules -granules r very fine -small in size -randomly distributed in cytoplasm -difficult to seen by Perussion stain -They r ↓↓ in Fe def. an. an. of chronic dis.	**↑Granulation**	**Ring Sideroblasts**
	Granules : -Larger -Numerous -Easily seen by Perussion blue	Mitochondria Fe

↑↑ Granulation

Parallel to % of saturation of Transferrin	Not parallel to % of sat. of Transferrin
As in Haemolytic anaemia Hemochromatosis Hemosiderosis	As in Thalasamia

Pathological alterations in Haem Synthesis

I- Sideroblastic Anaemia

Def:

Refractory dyserythropoietic anaemia (mainly 1ry acquired) characterized by:

- Variable no. of hypochromic cells in blood
- ↑ Fe stores
- ring sideroblasts in BM

Pathogenesis:

Haem Synthesis

Mitochondria:

Glycine+ succinyl Co A —(ALA synthase, vit B6)→ ALA ⟶

Porphobilinogen (PBG) ⟶ more steps (see porphyria) till it + Fe Haem

-Impaired haem synthesis due to a defect in protoporphyrin synthesis → Fe uptake by cells is not regulated when proyoporphyrin ↓ so, Fe continues to enter cell e' out utilization (Fe uptake by erythroblasts continues) → accumulation in mitochondria→ burst & form a ring over 1/3 circumference of the nucleus → Ring Sideroblast.

-These sideroblasts r unsuitable for circulation ⟶ accumulate in BM→ false impression of erythroid hyperplasia & destroyed in BM (Ineffective Erythropoiesis).

Ring Sideroblast:

3 criteria must be fulfilled:

- Fe granules must be abnormally large
- Must exceed 5-6 in no.
- Perinuclear arc must be around 1 or more of the nucleus
  3

❖ Defect in protoporphyrin synthesis is due to deficiency of enzymes needed for its synthesis

most common ALA synthase

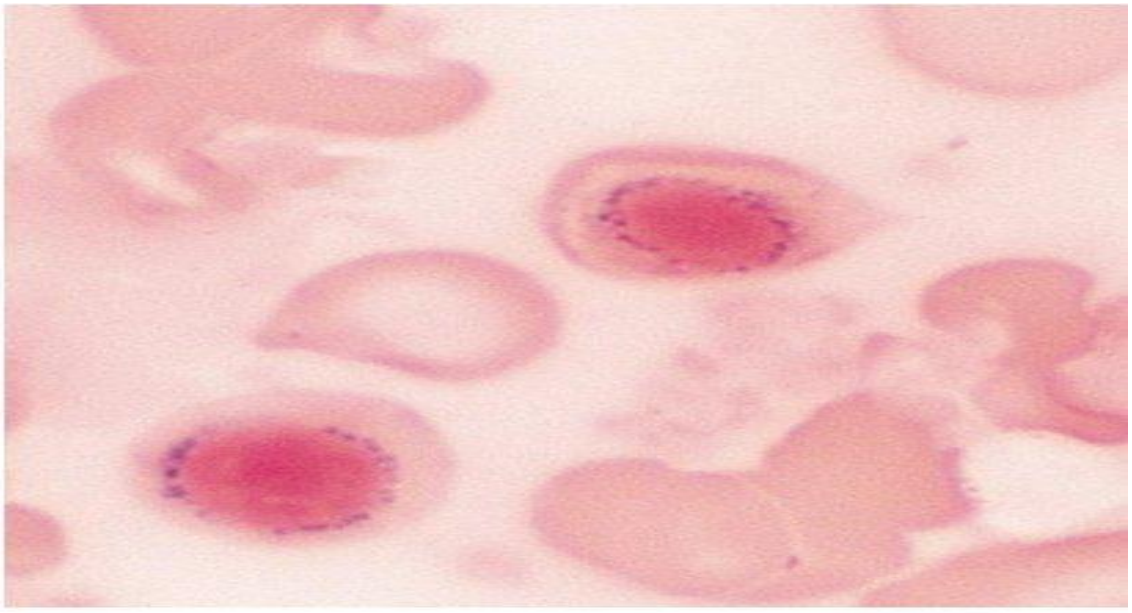
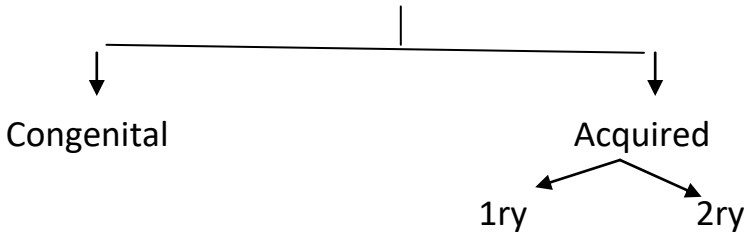


Figure 3.14 Ring sideroblasts with a perinuclear ring of iron granules in sideroblastic anaemia.

Classification of Sideroblastic Anaemia



A-Congenital (Inherited) Sideroblastic Anaemia

1- Sex linked sideroblastic an.

2-Mitochondrial DNA defect

3-Thiamine responsive sideroblastic an.

1-Sex linked Sideroblastic Anaemia

Incidence: **Rare**

Sex: **Male**

Age:

Detected during the 1st few weeks & months of life but sometimes detected in childhood & adolescence

Pathogenesis:

Missense point mutation of erythroid aminolaevuolinic acid synthase (δ ALA S) gene on X chromosome affecting pyridoxal (B6) binding site → ↓ sensitivity (affinity) of the enzyme for its co-enzyme (B6).

Diagnosis:

Clinical picture:

-Moderate or severe anaemia

-F carriers has mild Dimorphic picture (Normal, microcytic).

-Spleen may be enlarged

Lab findings:

1-CBC:

RBCs:

-MHA

↓MCV,↓MCHC,↓ MCH

↓Retics

few circulating sideroctes , normoblasts

WBC: may be↓ neutrophils due to enlarged spleen

platelets: may be↓ due to enlarged spleen

2-BM:

-Hypercellular (Erythroid Hyperplasia)

Iron stain:

- ↑ Fe stores
- ↑ siderotic granules in erythroblast
- many Ring sideroblasts > 15%

3- Blood chemistry:

-↑serum Fe

-↑Transferrin sat.

-↑serum ferritin

4- Hb electrophoresis: Hb A2 is N or ↓.

2-Mitochondrial DNA defect: (Rare)

It is due to a defect (mutation) of mitochondrial DNA ⟶ severe sideroblastic an. e macrocytic

RBCs & multi organ dysfunction.

3- Thiamine responsive sideroblastic anaemia:

Mitochondrial dysfunction but not in its DNA, defect is in Thiamine phosphokinase ⟶ ↓thiamine uptake

-AR -MCV N or ↑ macrocytes.

B- Acquired Sideroblastic Anaemia

1- Primary Acquired Sideroblastic Anaemia: (worst type)

Def:

It is a form of myelodysplasia (refractory an. e' ring sideroblasts).

Age: middle age & elderly

Sex: both

Pathogenesis:

A- Somatic mutation of red cell progenitor ⟶ fault of haem synthesis mainly at ALA synthase but may be at other point (patient lives & dies sideroblastic).

B- Somatic mutation affecting Pluripotent stem cell ⟶ abnormal RBCs, WBCs & platelets {Pre-Leukemic → may turn to AML}

Diagnosis: Lab. Findings:

1- CBC:

RBCs:

-macrocytic anaemia

-may be Dimorphic picture (macro,microcytes)

WBCs, platelets: N or affected.

Pre-Leukemic features:

- Pelger Huet phenomena (↓segmentation).
- hypogranular polymorphs
- ↓LAP score
- few myelocytes or blasts
- ↑monocytes
- ↓colony formation in agar.

2-Blood Chemistry:

- ↑ serum iron
- ↑ serum ferritin
- ↑transferrin saturation
- N TIBC

3- BM:

- marked erythroid hyperplasia.
- megaloblastic changes;

❖ **Fe stain:**

- ↑Fe stores.
- Ring sideroblasts (> 15%).

4-Chromosomal study: (only in 1ry acquired)

-Partial deletion or re-arangement of a group 19,20 chromosome.

-Monosomy 5 or 7.

-Mutation in RAS oncogene.

2- Secondary Acquired Sideroblastic Anaemia (best prognosis)

I-Vitamin B6 deficiency:

- ↓B6 ↑ Fe absorption ↑ serum Fe ↑ stores ↑ sideroblasts

Pathogenesis:

vit B6 (pyridoxal phosphate) is a co-enzyme for ALA synthetase, imp. for Haem synthesis.

Aeitology:

- coelic disease (↓abs.)

-pregnancy (consumption,↑loss).

- Haemolytic an. (consumption).

Associated folate def. ↑Tendency to form ring sideroblasts.

II- Vitamin B6 antagonists:

Anti tuberculous drugs esp. Isoniasid

III- Disturbed Haem synthesis:

- Alchoholism
- Chloramphenicol
- Erythropoietic porphyria
- Lead posioning
- Others: malignancy,R.A

IV- Haematoological causes:

-Myeloproliferative disorders (MPD).

-Lymphoproliferative disorders.

- Pernicious anaemia.

-Haemolytic anaemia.

Lab. Investigations:

CBC, BM, chemistry: as 1ry acquried.

Treatment of sideroblastic anaemia:

-1ry acq.: refractory to all forms of therapy.

-Inherited type: partially responsive to vit. B6.

-2ry types: are mostly cured.

Because of problems of iron overload, blood transfusion & iron therapy must be avoided.

Treatment:

1- Pyridoxine: (50-100 mg/d)

About 1/3 of patients whether acq. or congenital show **partial response:**

Partial ↑ retics, Hb.

But hypochromic cs & ring sideroblasts remains.

Complete response:

Seen in alcoholism, coeilic dis., anti-tuberculous ttt.

2- Folic acid:

Folate deficency is common due to marrow erythroid turnover (ineffective erythropoiesis) esp. in 2ry sid. an.

So Folic acid must be tried in every case except 1ry acquired.

Anaemia of Chronic Diseases

Def:

One of the commonest types of anaemia found in many diseases.

Aeitology:

-T.B

- Malignancy

-Chronic inflammatory diseases

-Connective tissue dis. E.g. R.A

- Renal diseases.

All above diseases ↓ Fe, ↓ folate but 3 main abnormalities:

1- Shortened RBCs survival.

2- ↓ BM response.

3- Disturbed Fe metabolism.

3- Disturbed Fe metabolism:

-Lactoferrin release → + Fe → interferes e' Fe reutilization.

-Slow release of Fe from MQ (stores).

- ↑ Apoferritin synthesis (acute phase reactant).

- ↓ Transferrin R. on erythroblast as in R.A.

2- BM response:

- ↓ Epo as in renal dis.

- ↓ Erythropoiesis e.g. R.A → serum factors → ↓ erythroid colonies.

1-Shortened RBCs survival:

-MQ r active cleaning even minimally damaged RBCs.

- ↑Urea → defect in environment→ haemolysis of RBCs.

Diagnosis:

-History of a disease.

- C/P of a disease.

-Lab. Findings:

CBC:

NNA or MHA.

BM:

-↑ Fe in MQ.

- ↓ sideroblasts.

Blood chemistry:

-↓ serum Fe.

- ↓ Transferrin sat.

- TIBC N or↓

- serum ferritin N or ↑

In summary:

Defective Fe reutilization:

Accumulation of Fe in stores (MQ), but doesn't reach erythroid:

- ↓serum Fe.
- ↓sideroblasts.
- ↑ stores,↑ ferritin.

Lead Poisoning

Aeitology:

Exposure to lead:

-working in lead industeries e.g. battery manufacturing.

- motor car building.

- painters

- childern chewing lead toys or articles painted e' lead.

Pathogenesis:

- ↓ marrow erythropoiesis, haematopoiesis ⟶ Aplasia.

- direct RBCs membrane damage ⟶ H.A.

- inhibit haem synthesis.

- inhibit globin synthesis.

- inhibit Pyrimidine -5- nucleotidase w' cleaves residual nucleotides⟶ **Basophilic Stippling.**

Diagnosis:

- History

- C/P:

  - colics, constipation.

  - Grey lines on teeth.

  - White lines on bone epiphysis (X- ray).

- Lab:

CBC:

- Mild to moderate NNA or MHA.

-slight ↑ retics.

-Basophilic stippling

-sometimes few normoblasts (due to haemolysis).

WBC: N

BM:

- Erythroid hyperplasia e' bsophilic stippling.

- Ring sideroblasts (2ry sid. An.).

Basophilic Stippling:

-accumulation of: ribosomal aggregates & Mitochondrial fragments

-Seen in RBCs by Leishman stain

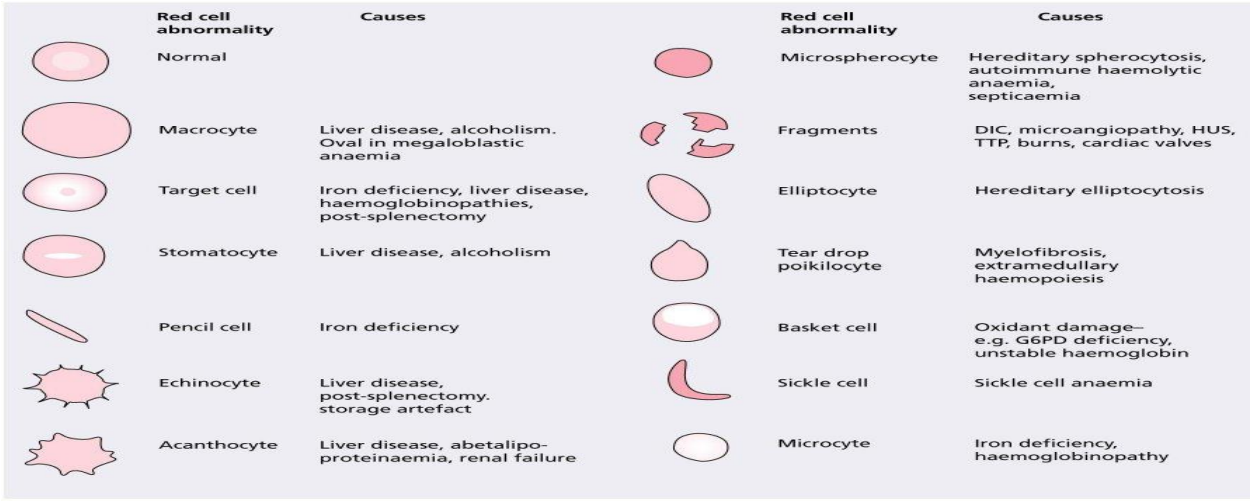
-Found in (causes):

- Immature RBCs (immediately after nuclear extraction) .

- Pyrimidine – 5- nucleotidase w' cleaves residual nucleotides.

- Lead poisoning w' inhibits this enzyme.

- Dyserythropoiesis= Ineffective erythropoiesis.



Red cell abnormality	Causes	Red cell abnormality	Causes
Normal		Microspherocyte	Hereditary spherocytosis, autoimmune haemolytic anaemia, septicaemia
Macrocyte	Liver disease, alcoholism. Oval in megaloblastic anaemia	Fragments	DIC, microangiopathy, HUS, TTP, burns, cardiac valves
Target cell	Iron deficiency, liver disease, haemoglobinopathies, post-splenectomy	Elliptocyte	Hereditary elliptocytosis
Stomatocyte	Liver disease, alcoholism	Tear drop poikilocyte	Myelofibrosis, extramedullary haemopoiesis
Pencil cell	Iron deficiency	Basket cell	Oxidant damage– e.g. G6PD deficiency, unstable haemoglobin
Echinocyte	Liver disease, post-splenectomy. storage artefact	Sickle cell	Sickle cell anaemia
Acanthocyte	Liver disease, abetalipo-proteinaemia, renal failure	Microcyte	Iron deficiency, haemoglobinopathy

Figure 2.16 Some of the more frequent variations in size (anisocytosis) and shape (poikilocytosis) that may be found in different anaemias. DIC, disseminated intravascular coagulopathy; G6PD, glucose-6-phosphate dehydrogenase; HUS, haemolytic uraemic syndrome; TTP, thrombotic thrombocytopenic purpura.

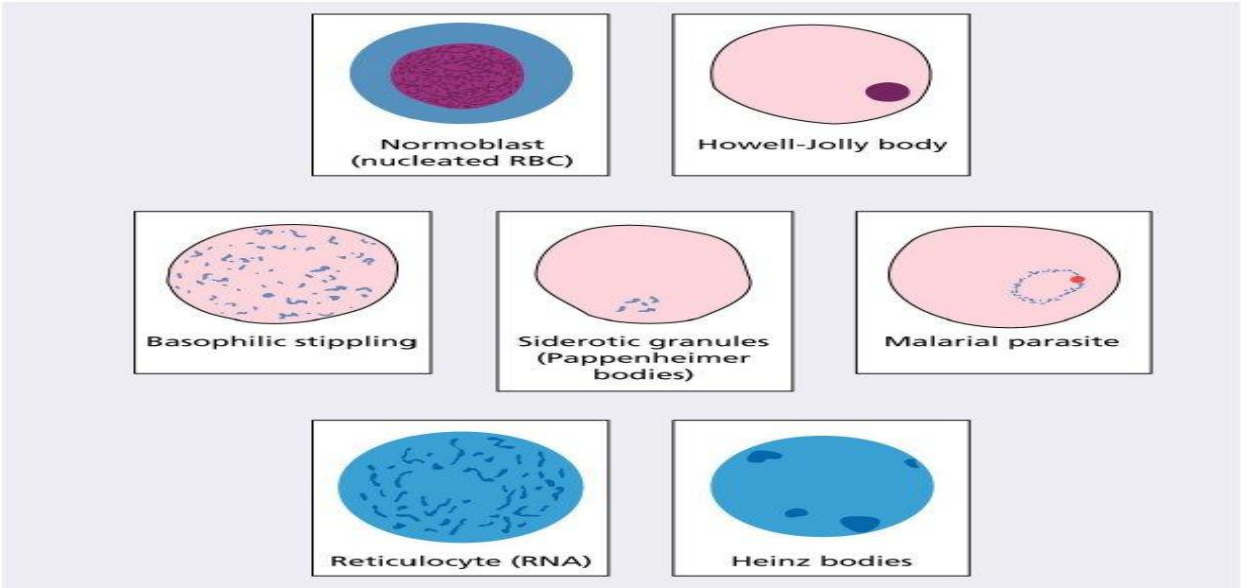
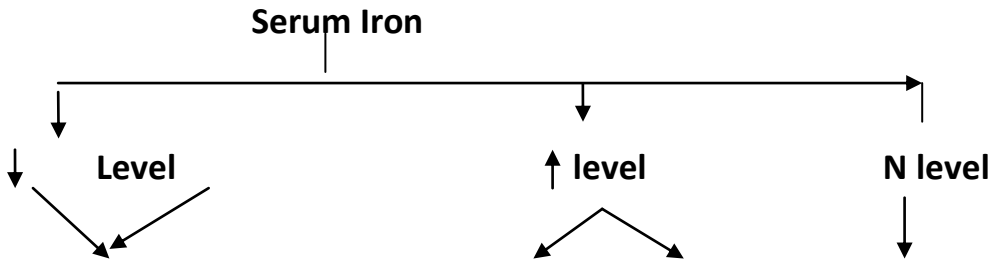


Figure 2.17 Red blood cell (RBC) inclusions which may be seen in the peripheral blood film in various conditions. The reticulocyte RNA and Heinz bodies are only demonstrated by supravital staining (e.g. with new methylene blue). Heinz bodies are oxidized denatured haemoglobin. Siderotic granules (Pappenheimer bodies) contain iron. They are purple on conventional staining but blue with Perls' stain. The Howell–Jolly body is a DNA remnant. Basophilic stippling is denatured RNA.

Table 1: D.D of Microcytic hypochromic Anaemia



	Fe def anaemia	An. Of chronic disease	Sideroblastic anaemia	Thalasamia major	Thalasamia minor
-serum Fe:	↓	↓	↓	↓	N
-Transferrin sat.	↓	↑	↑	↑	N
-TIBC:	↑	↑	N	N	N
-serum ferritin:	↑	↑	↑	N or ↓	N
- BM Fe stores:	↓	↑	↑	↑	↑
-Indices: MVV,MCH,MCHC:	↓	Low N or mild reduction	Very low in cong. Type,but ↑ MCV often in acquired	↓ All reduced & very low for the degree of anaemia ↑	
-Hb electrophoresis:	N	N	N	F,A2	
-Erythropblast Fe (sideroblast):	Absent	Absent	Ring sideroblast	present	