Bone marrow failure

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Pancytopenia :

Pancytopenia describes a reduction in the blood count of all the major cell lines-red cells,white cell and platelets. It has several causes which can be broadly divided into: **decreased bone marrow production** or **increased peripheral destruction.**

Aplastic (hypoplastic) anaemia:

It is defined as pancytopenia resulting from aplasia of the bone marrow in the absence of an abnormal infiltrate and with no increase in reticulin.

it is classified into:

1. primary: congenital or acquired.
2. secondary types.

Primary

Congenital (Fanconi and non-Fanconi types)

idiopathic acquired

Secondary

Ionizing radiation: accidental exposure (radiotherapy, radioactive isotopes,

nuclear power stations)

Chemicals: benzene, organophosphates and other organic solvents, DDT and other

pesticides, organochlorines, recreational drugs (ecstasy)

Drugs

those that regularly cause marrow depression (e.g. busulfan, cyclophosphamide,

anthracyclines, nitrosoureas)

Those that occasionally or rarely cause marrow depression (e.g. chloramphenicol,

sulphonamides, gold, anti-inflammatory, antithyroid, psychotrophic,

anticonvulsant!antidepressant drugs)

Viruses: viral hepatitis (non-A, non-B, non-C, non-G in most cases), EBV

Pathogenesis:

The underlying defect in all cases appears to be a substantial reduction in the number of haemopoietic pluripotential stem cells, and a fault in the remaining stem cells or an immune reaction against them, which makes them unable to divide and differentiate sufficiently to populate the bone marrow .A primary fault in the marrow microenviromnent has also been suggested.

Congenital:

The Fanconi type:

It has an autosomal recessive pattern of inheritance and is often associated with:

_ growth retardation

_congenital defects:

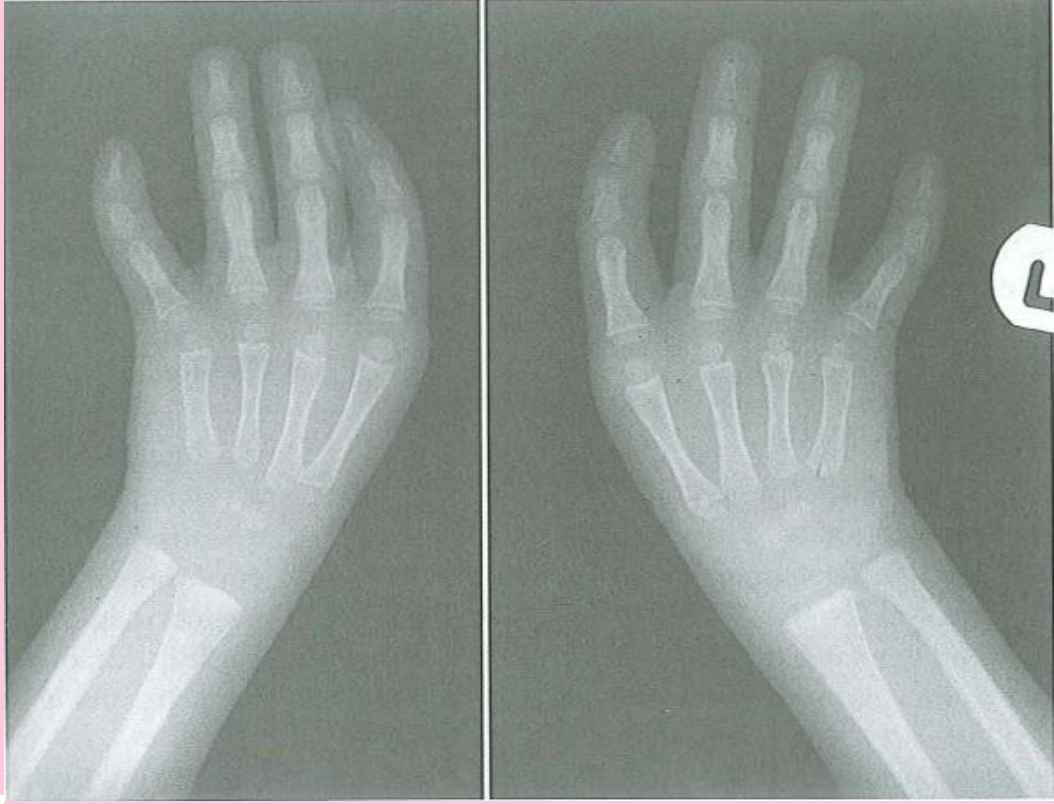
*of the skeleton (e.g. microcephaly, absent radii or thumbs)

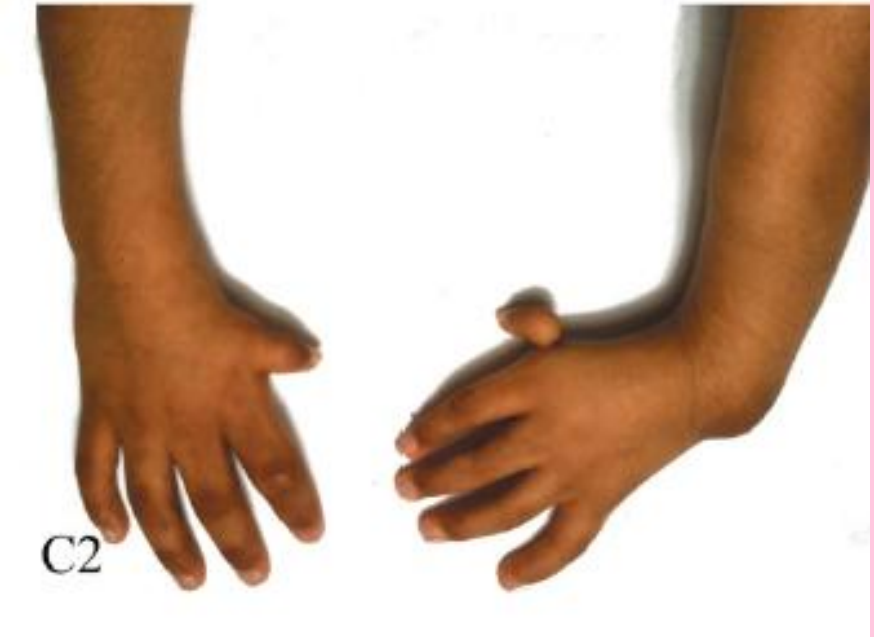
* of the renal tract (e.g. pelvic or horseshoe kidney)

* or skin (areas of hyper- and hypopigmentation)

_sometimes there is mental retardation.

The encoded proteins of the affeected gene cooperate in a common cellular pathway involved in DNA repair so cells from Fanconi's anaemia (FA) patients show an abnormally high frequency of spontaneous chromosomal Breakage

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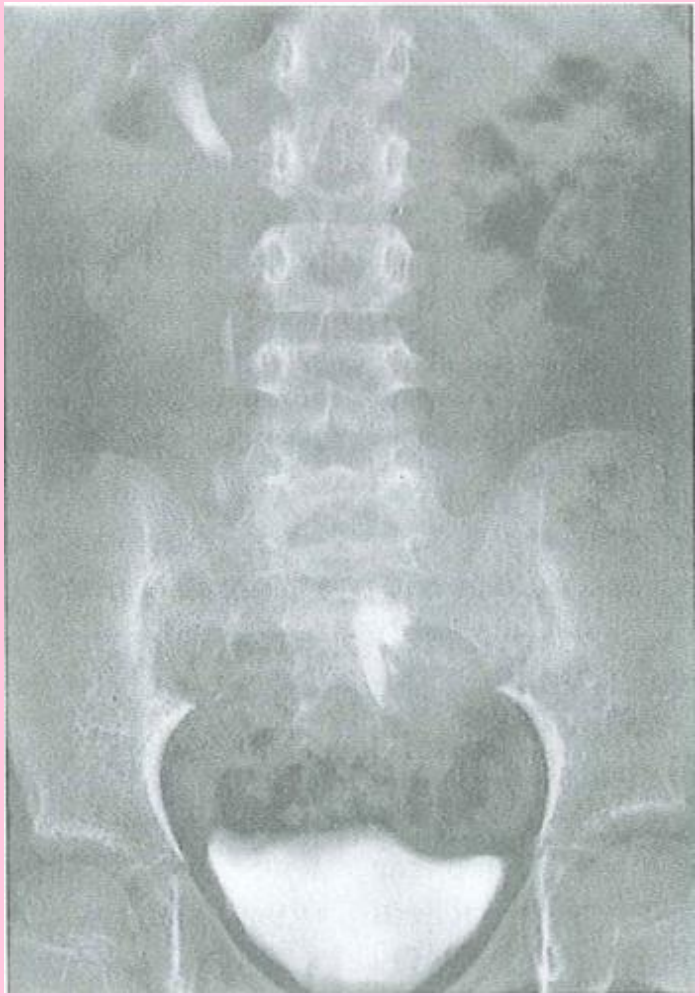
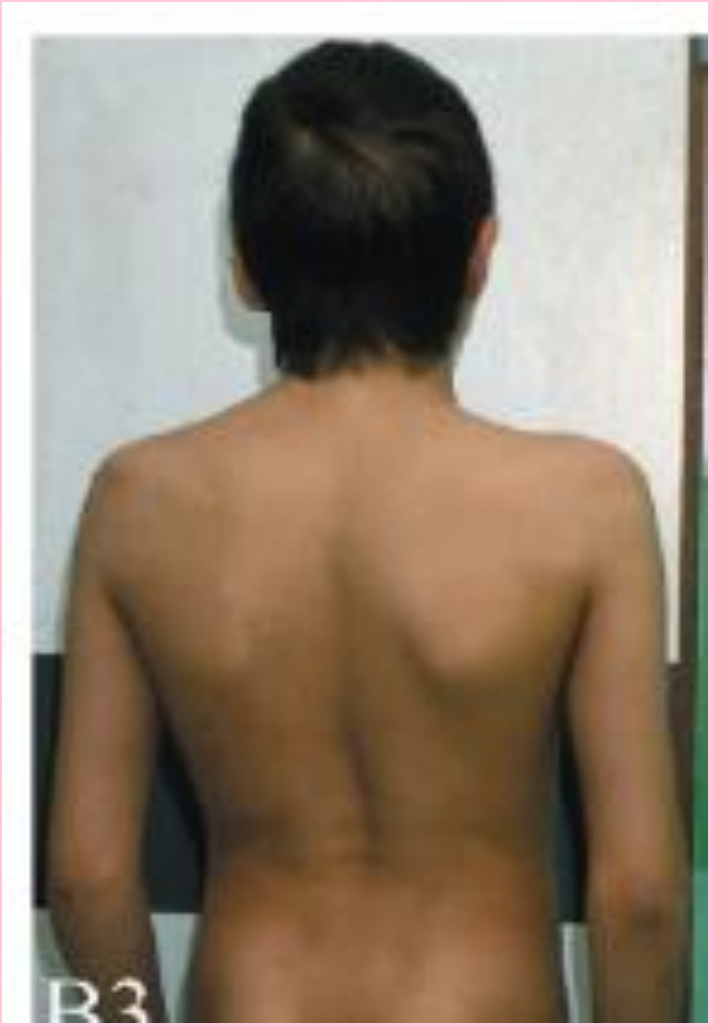



B3

The usual age of presentation of FA is 5-10 years.

the diagnostic test is elevated breakage after incubation of peripheral blood lymphocytes with the DNA cross-linking agent diepoxybutane (DEB test).

Approximately,10% of cases develop acute myeloid leukaemia.

Dyskeratosis congenita(DC):

is a rare sex linked disorder with:

_ nail and skin atrophy.

_a high risk of cancer.

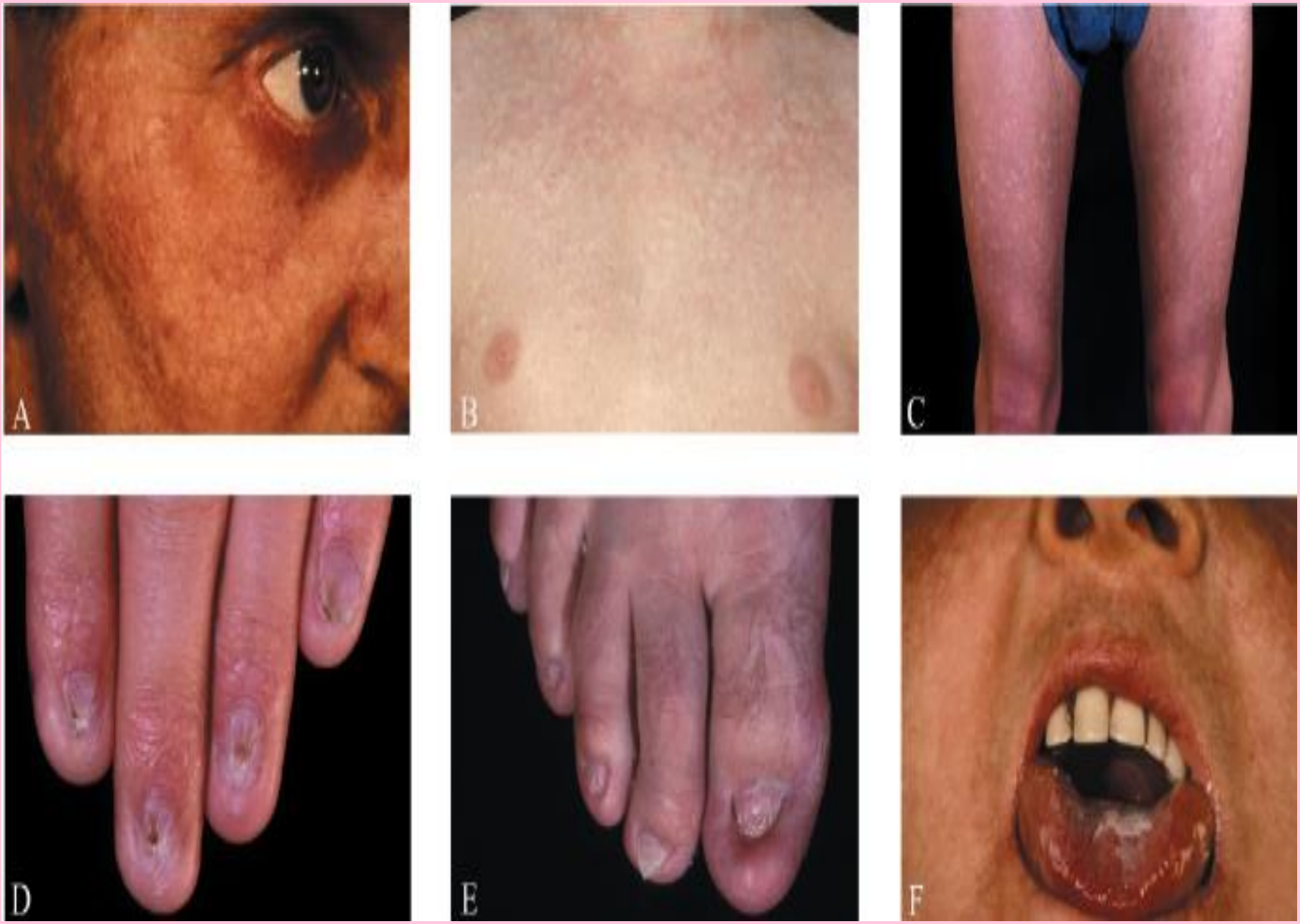
it is associated with mutations in the:

_ *DKCl (dyskerin),or*

_*TERC (telomerase reverse transcriptase RNA*

template) genes which are both involved in the maintenance of telomere length,so deficiency in stem cell activity due to defective telomerase activity.

The demonstration of *DKC1 and TERC mutations in DC families provides an accurate* diagnostic test


A
B
C
D
E
F

Other inherited bone marrow failure syndromes:

Diamond_Blackfan anemia (DBA)

Shwachman_Diamond syndrome(SDS)

Sever congenital neutropenia

Amegakaryocytic thrombocytopenia & thrombocytopenia with abscent radii.

In DC,DBA & SDS there is a defect in ribosomal biosynthesis & function.

Idiopathic acquired:

This is the most common type of aplastic anaemia,accounting for at least two-thirds of acquired cases..

In most cases haemopoetic tissue is the target of an immune process dominated by oligoclonal expression of cytotoxic T cells which secrete y-interferon and tumour necrosis factor.

In approximately onethird of cases short telomeres are found in leucocytes, especially in those with a prolonged clinical course. Mutations in the telomere repair complex have been described but their relevance is unclear.

The favourable responses to antilymphocyte globulin (ALG) and cyclosporine support the concept that autoimmune T-cell mediated damage, possibly against functionally and structurally altered stem cells.

Secondary:

_This is often caused by:

direct damage to the haemopoietic marrow by radiation or cytotoxic drugs.

The antimetabolite drugs (e.g. methotrexate) and,

mitotic inhibitors (e.g. daunorubicin) cause only

temporary aplasia but the alkylating agents, particularly busulfan, may cause chronic aplasia closely resembling the chronic idiopathic disease.

_Some individuals develop aplastic anaemia as a rare idiosyncratic side-effect of drugs such as chloramphenicol or gold which are not known to be cytotoxic.

_Chemicals such as benzene may be implicated .

_Rarely aplastic anaemia may be the presenting feature

of acute lymphoblastic or myeloid leukaemia, especially in childhood. Myelodysplasia may also present with a hypoplastic marrow.

Clinical features:

The onset is at any age with a peak incidence around 30 years and a slight male predominance; it can be insidious or acute with symptoms and signs resulting from anaemia, neutropenia or thrombocytopenia.

_Infections, particularly of the mouth and throat, are common and generalized infections are frequently life-threatening.

_ bruising, bleeding gums, epistaxes and menorrhagia are the most frequent haemorrhagic manifestations and the usual presenting features.

_ symptoms of anaemia.

_The lymph nodes, liver and spleen are not enlarged

Laboratory findings:

1 . Anaemia is normochromic, normocytic or macrocytic (mean cell volume (MCV) often 95-110 fL).

The reticulocyte count is usually extremely low in relation to the degree of anaemia.

2 .Leucopenia. There is a selective fall in granulocytes usually but not always to below 1.5 x 109/L.

In severe cases, the lymphocyte count is also low.

3 .Thrombocytopenia is always present .

4 .There are no abnormal cells in the peripheral blood.

5 . The bone marrow shows hypoplasia, with loss of haemopoietic tissue and replacement by fat which comprises over 75% of the marrow. Trephine biopsy may show patchy cellular areas in a hypocellular background The main cells present are lymphocytes and plasma cells; megakaryocytes in particular are severely reduced or absent.

Severe cases show:

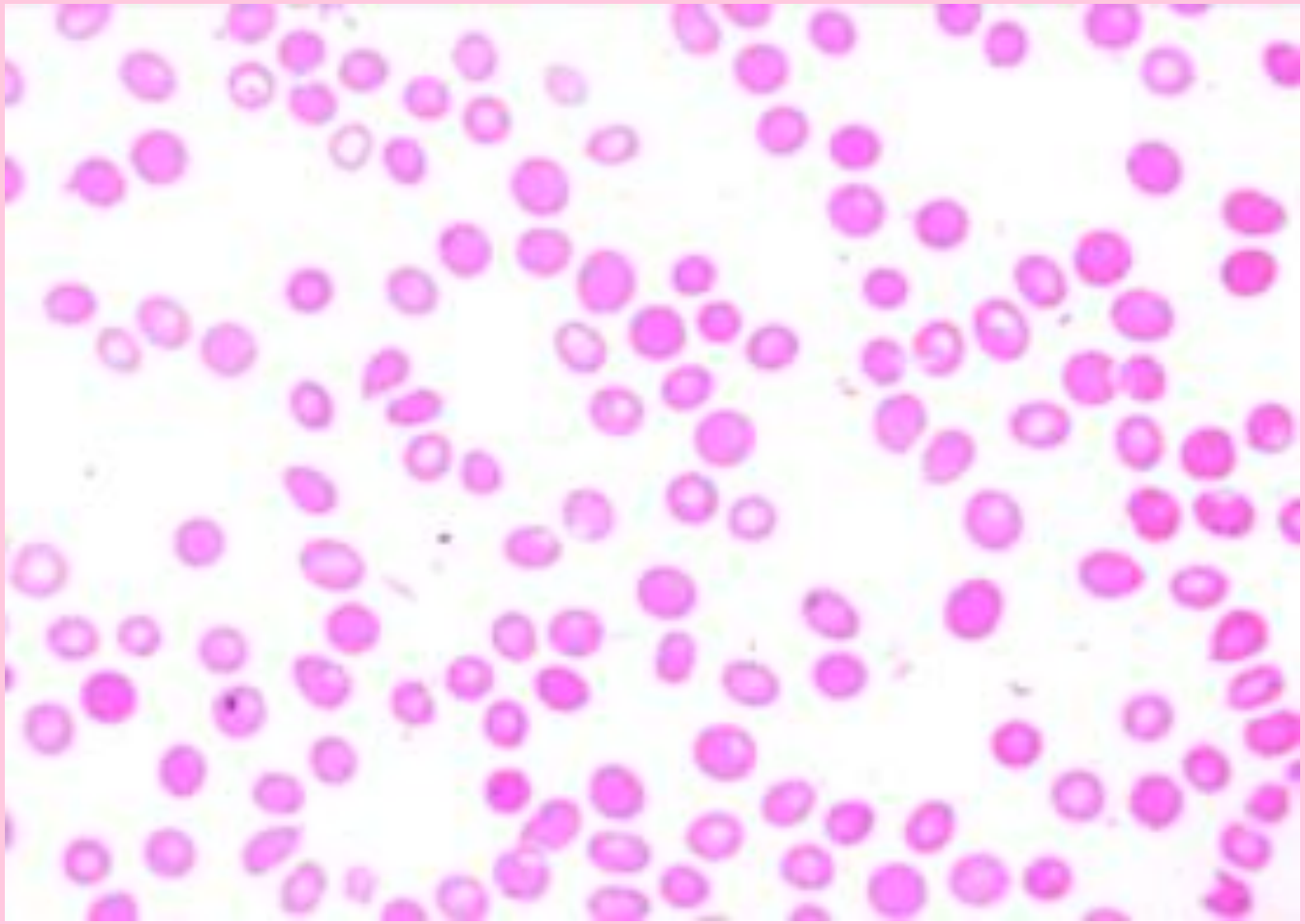
neutrophils <0.5 x 109/L (very severe <0.2 x 109/L)

platelets <20 x 109

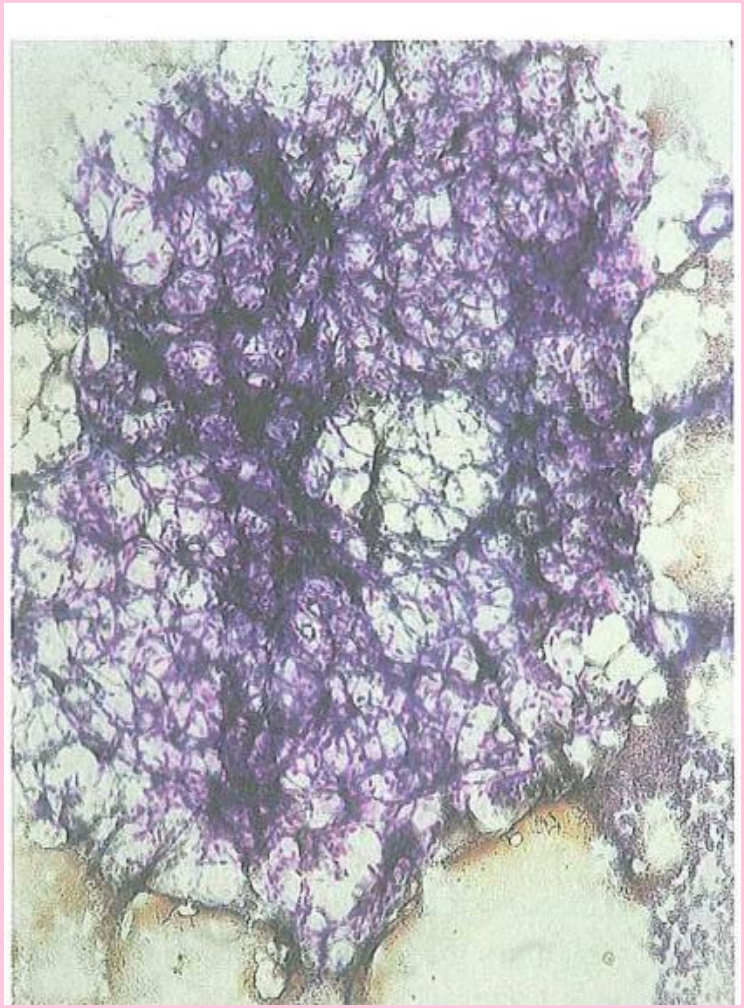
reticulocytes <20 x 109/L

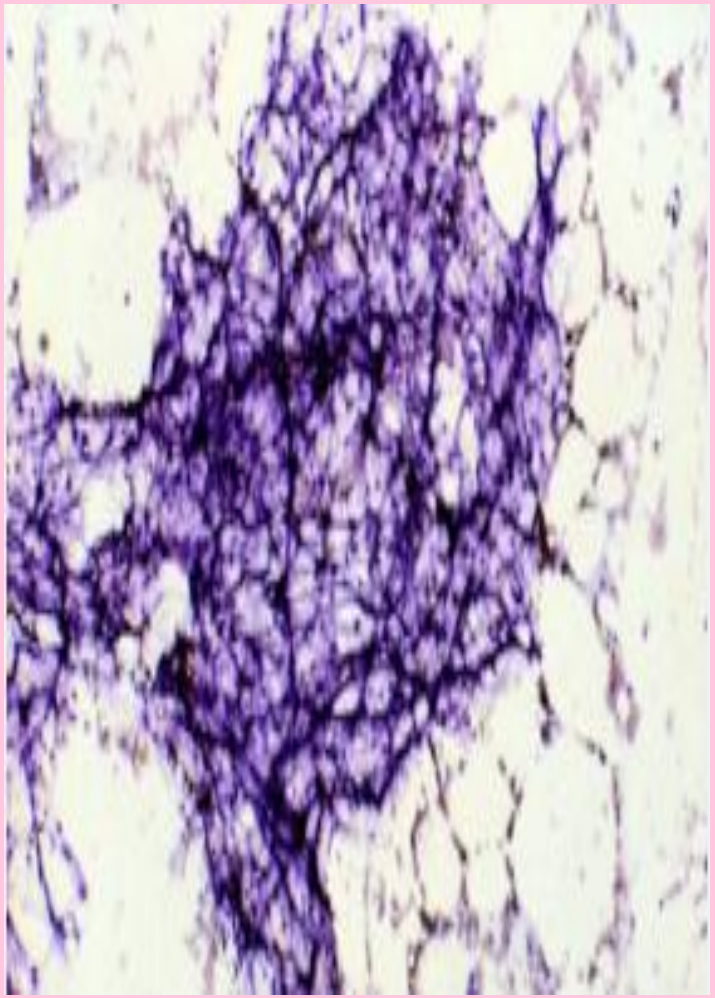
and marrow cellularity <25%

Blood film

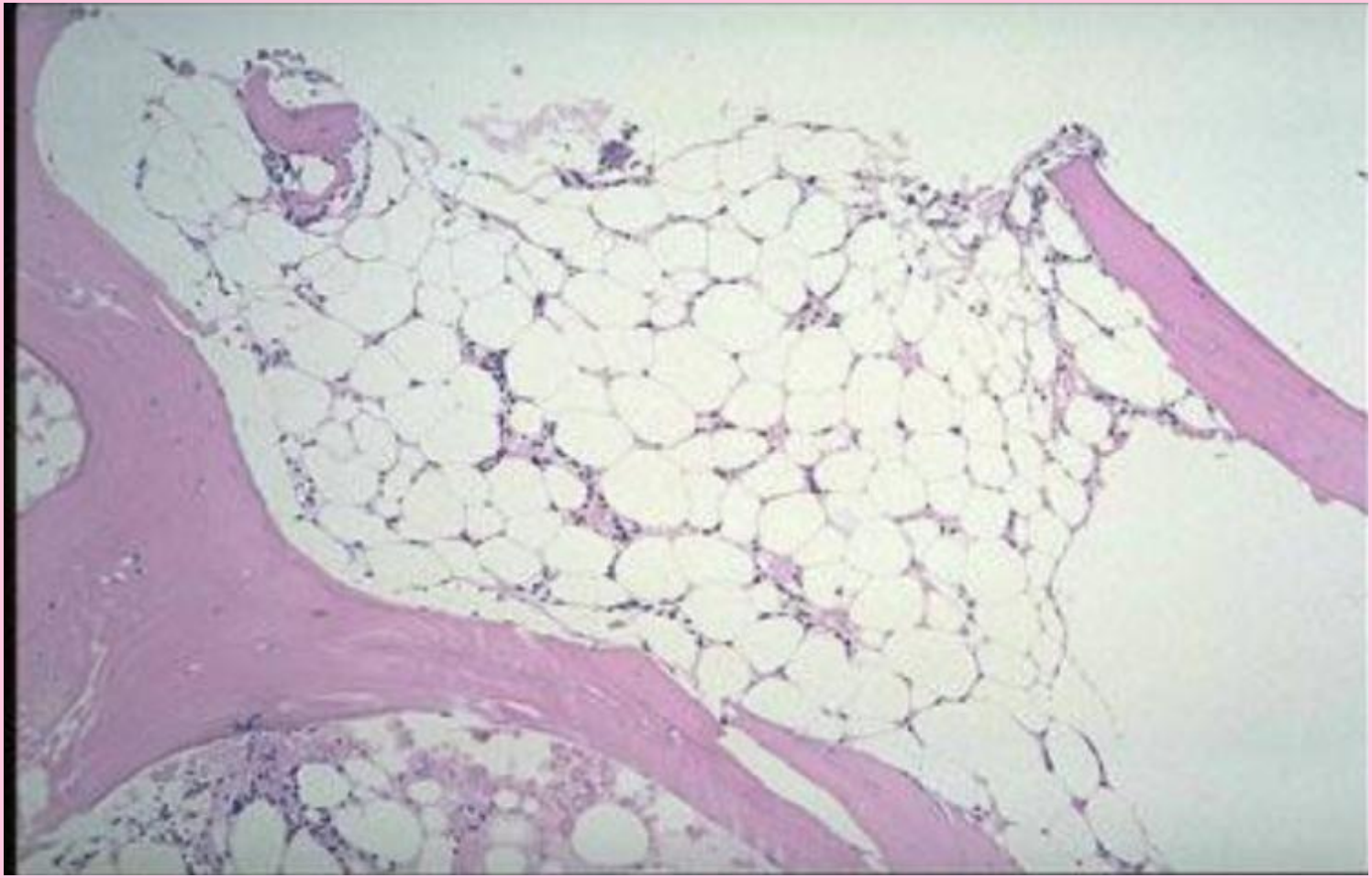


low power views of bone marrow show severe reduction of haemopoietic cells with an increase in fat spaces





Trephine biopsy



Differential diagnosis:

Decreased bone marrow function:

Acute leukaemia, myelodysplasia, myeloma

Infiltration with lymphoma, solid tumours, tuberculosis

Megaloblastic anaemia

Paroxysmal nocturnal haemoglobinuria

Myelofibrosis

Haemophagocytic syndrome

Increased peripheral destruction:

Splenomegaly(hypersplenism)

Diagnosis:

The disease must be distinguished from other causes of pancytopenia and this is not usually difficult provided _an adequate bone marrow sample is obtained.

_Cytogenetic analysis should be performed.

_Paroxysmal nocturnal haemoglobinuria (PNH) must be excluded by flow-cytometry testing of red cells for CD55 and CD59.

In older patients,hypoplastic myelodysplasia may show similar appearances.

Qualitative abnormalities of the cells and clonal cytogenetic changes suggest myelodysplasia rather than aplastic anaemia.

Some patients diagnosed as having aplastic anaemia develop

PNH, myelodysplasia or acute myeloid leukaemia

in subsequent years.

Red cell aplasia:

1. Acute, transient:

a_Parvovirus B19 infects red cell precursors and causes a transient (5-10 days) red cell aplasia with the rapid onset of severe anaemia in patients with pre-existing shortened red cell survival

(e.g. sickle cell disease or hereditary spherocytosis);

b_Transient red cell aplasia with anaemia may also occur in association with drug therapy (e.g. azathioprine, co-trimoxazole),

c_and in normal infants or children, often with a history of a viral infection in the preceding 3 months.

2. Chronic form:This is a syndrome characterized by anaemia with normal leucocytes and platelets and reduced or absent erythroblasts in the marrow. The congenital form is known as: Diamond-Blackfan syndrome :

_It is inherited as a recessive condition.

_associated with a varying number of somatic disorders (e.g. of the face or heart).

_The median age at presentation is 8 weeks and 93% of patients presented in the first year of life.

_Mutation of a gene on chromosome 19 that encodes a ribosomal protein underlies some cases.

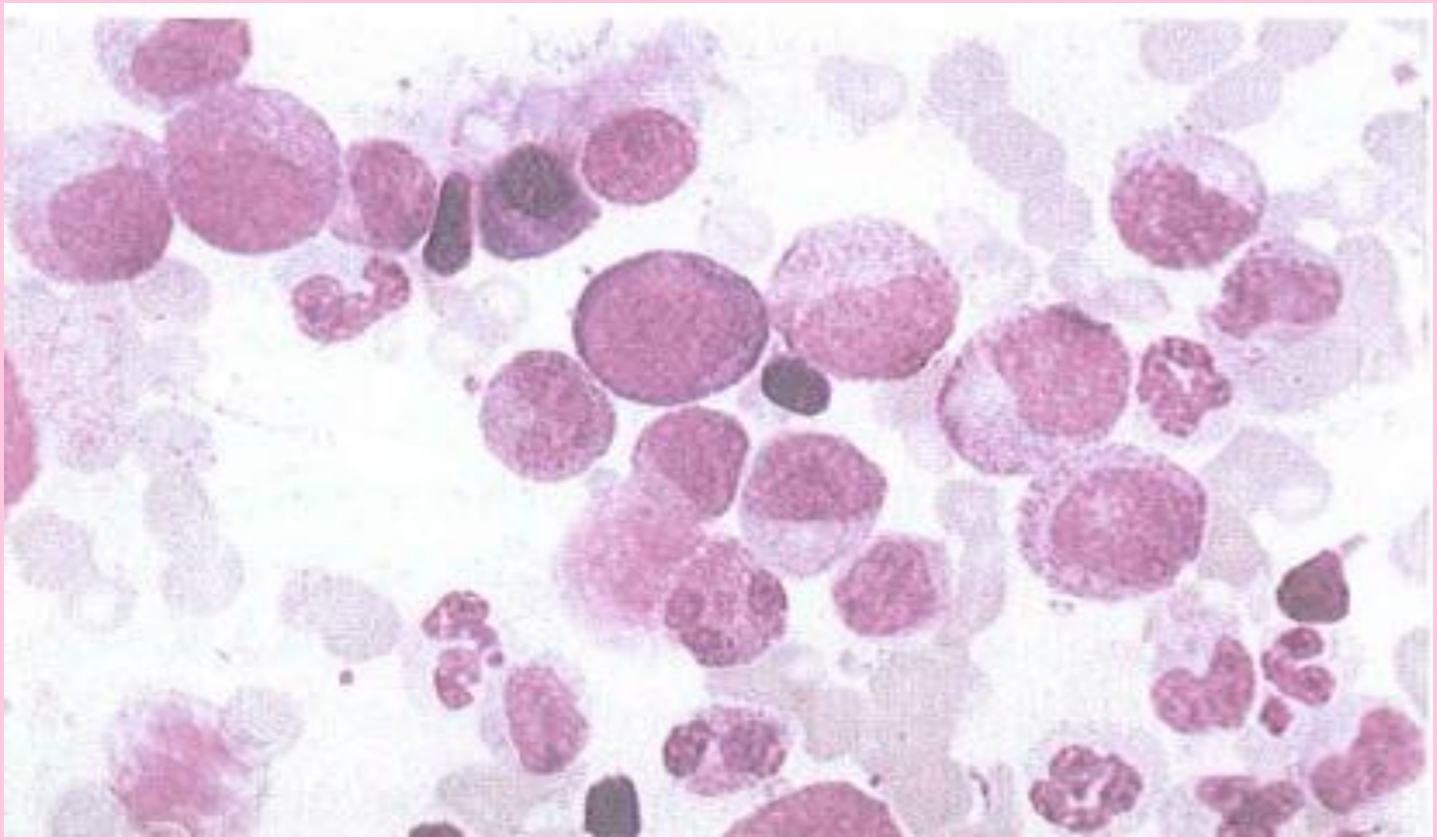
The acquired chronic form:

_ can occur without any obvious associated disease or precipitating factor (idiopathic).

_may be seen with autoimmune diseases (especially systemic lupus erythematosus),with a thymoma, lymphoma or chronic lymphocytic leukaemia.

_Red cell aplasia from anti-erythropoietin antibodies has been rarely described in patients with chronic renal failure receiving recombinant erythropoietin.

selective loss of erythropoiesis



Congenital dyserythropoietic anaemia:

a group of hereditary refractory anaemias characterized by:

_ ineffective erythropoiesis.

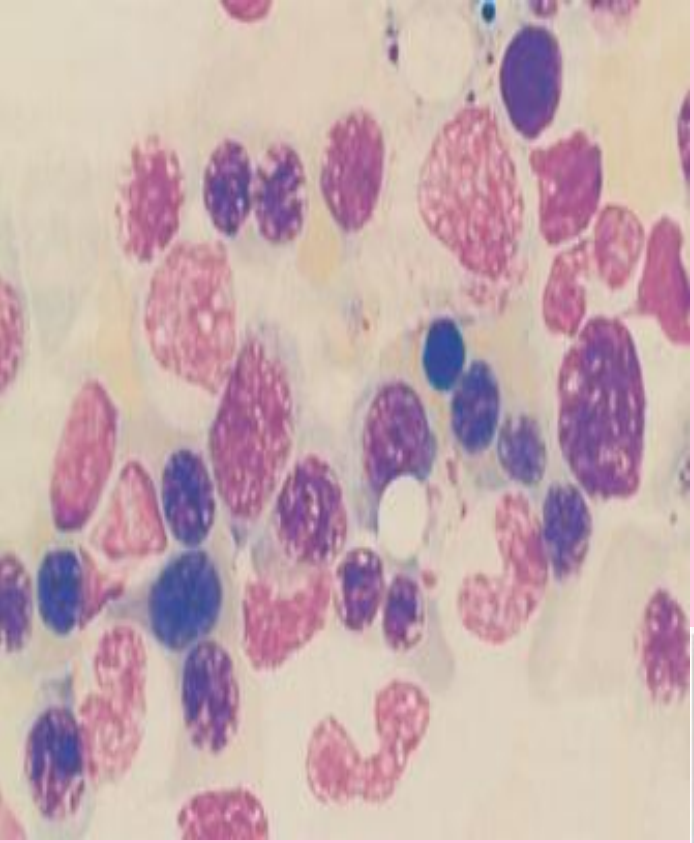
_internuclear bridging in normoblasts , erythroblast multinuclearity and Giant multinucleated erythroblast .

_The patient may be jaundiced with bone marrow expansion.

_ The white cell and platelet counts are normal.

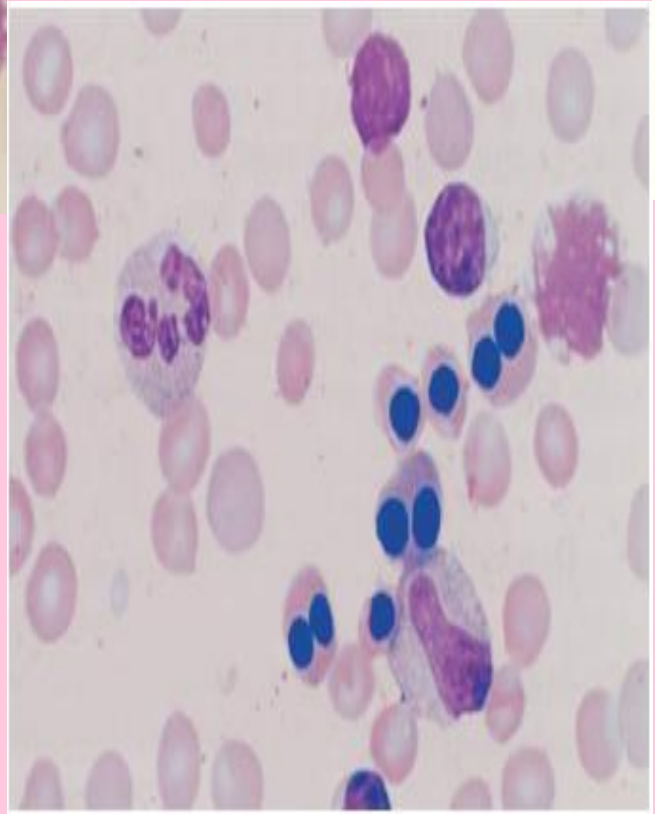
_ The reticulocyte count is low for the degree of anaemia, despite increased marrow cellularity.

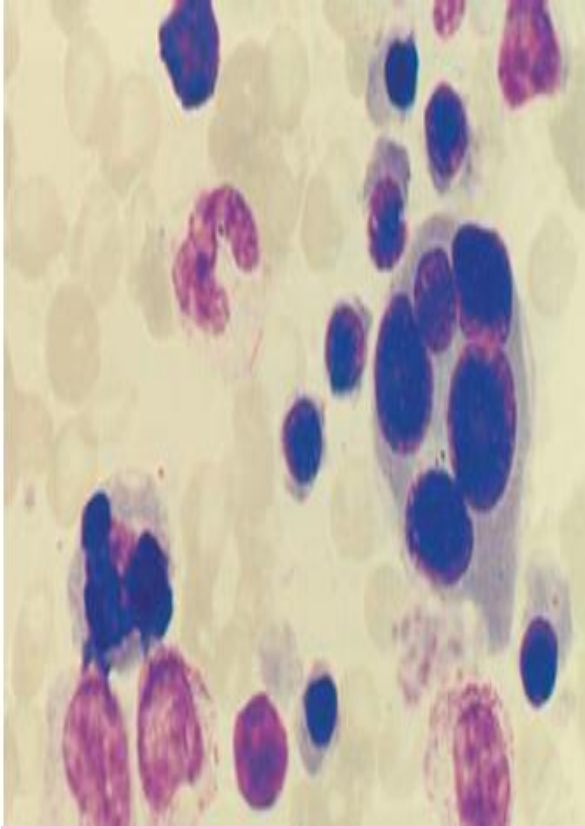
The anaemia is of variable severity and is usually first noted in infancy or childhood.



internuclear bridging in normoblasts

multinuclearity.





Giant multinucleated erythroblast


Thank you
Http://maomao520.yeah.net