APPROACHING TO PANCYTOPENIA

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PANCYTOPENIA

- Reduction in all 3 cell lines of blood;

- Hemoglobin < 13.5 (M)/ 11.5 (F) g/dl
- Total leukocyte count < 4000 /cumm
- Platelet < 150,000/cumm

PANCYTOPENIA

- **Haemoglobin of < 9 gm/dl**
- **WBC < 4,000/cmm**
- **Platelets < 100,000/cmm**

- **Severe pancytopenia**
  absolute neutrophil count < 500/cmm
  platelet count < 20,000/cmm
  corrected reticulocyte count < 1%

Ajai Kumar Garg, AK Agarwal, GD Sharma
www.apiindia.org/pdf/medicine_update_2017/mu_095.pdf

DEFINITION

- Cytopenia: reduction in either of the cellular component of blood

- Bicytopenia: reduction in any of the 2 cell lines of blood;
- Anemia plus thrombocytopenia
- Anemia plus leukopenia
- Thrombocytopenia plus leukopenia

CAUSES OF PANCYTOPENIA

- Normal adult marrow produces about

  $170x10^9$ RBC
  $100x10^9$ neutrophils
  $200x10^9$ platelets daily

- Defects in the stem cells or in the stroma or microenvironment of bone marrow can lead to bone marrow failure and pancytopenia

CAUSES OF PANCYTOPENIA

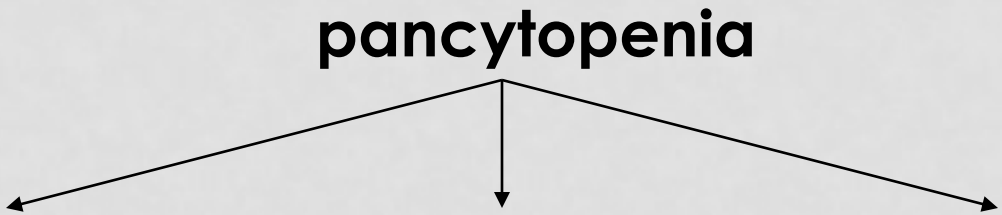
Bone marrow failure

Ineffective bone marrow production

Marrow space occupying lesions

Peripheral destruction of hematopoietic cells

APPROACH TO PANCYTOPENIA



increased destruction

- immune
- sepsis

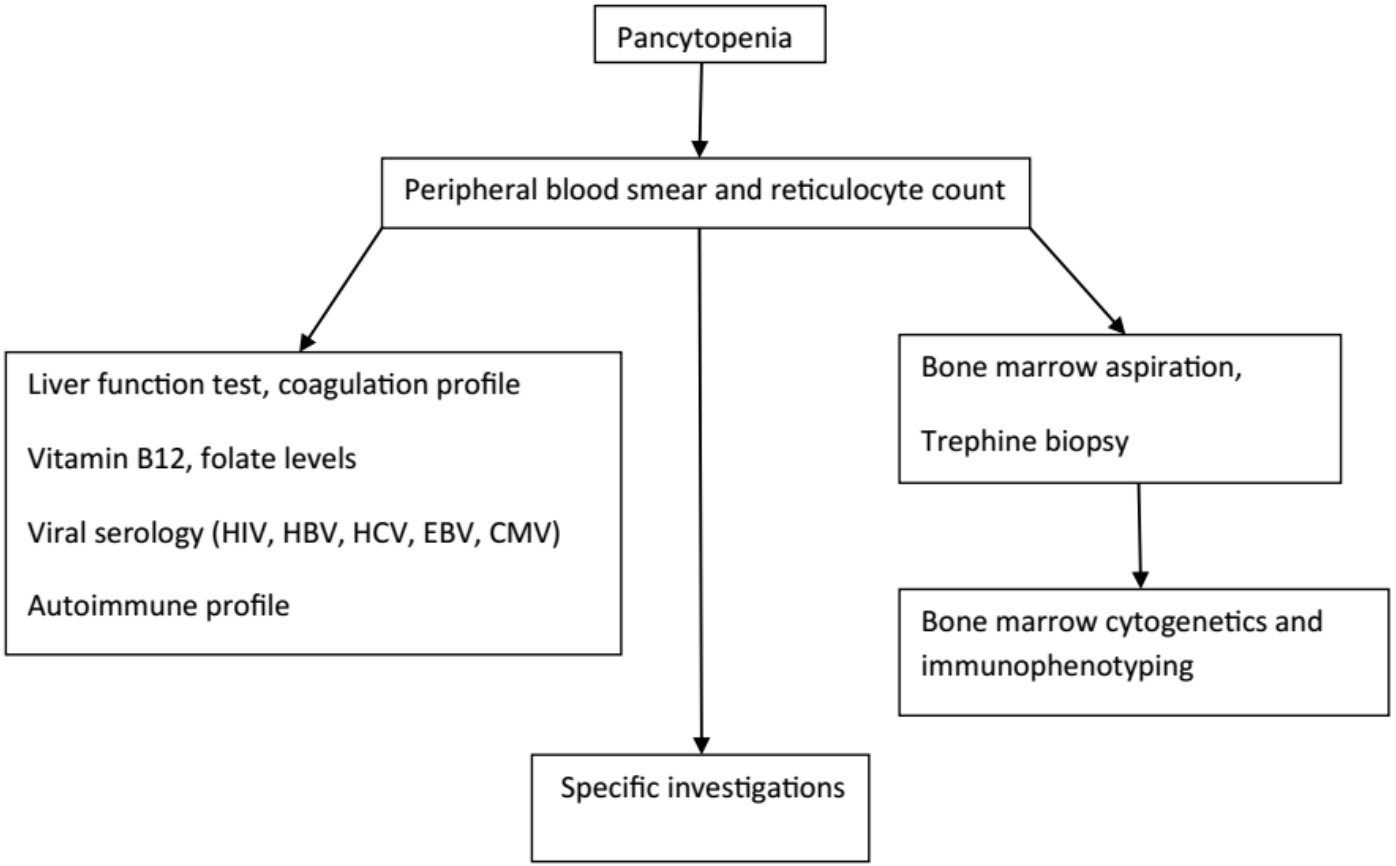
sequestration

- hypersplenism

decreased production

- MDS
- infiltration
- B12 def
- AA
- drugs
- viruses
- radiation

FLOW FOR EVALUATION OF PANCYTOPENIA



A PRACTICAL APPROACH

pancytopenia

↓

spleen
sepsis
retics, B12/folate, ANA, abdo U/S

↓

bone marrow

↙ ↘

hypocellular | hypercellular

POINTS TO CONSIDER IN HISTORY

- Age
- Sex
- Duration of symptoms
- Bone pains, fever, night sweats, malaise, weight loss
- Bleeding from any site
- Jaundice
- Joint pain, rash, photosensitivity
- Any radiation exposure

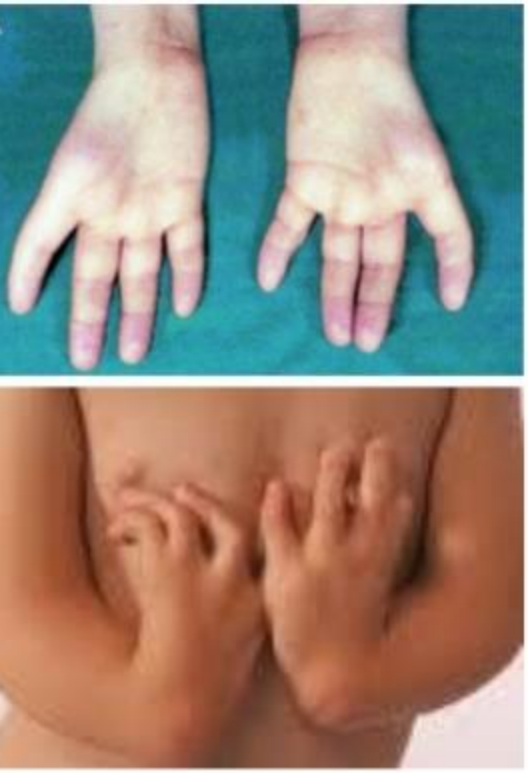
POINTS TO CONSIDER IN HISTORY

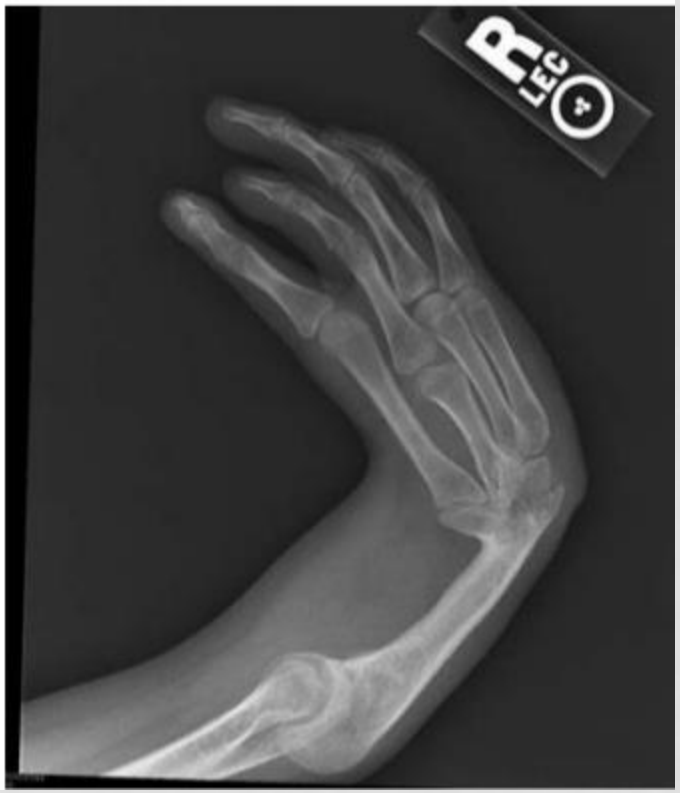
- Exposure to potentially toxic chemicals
- Treatment history including herbals and drug intake, blood transfusions
- Dietary history
- Occupational exposure history

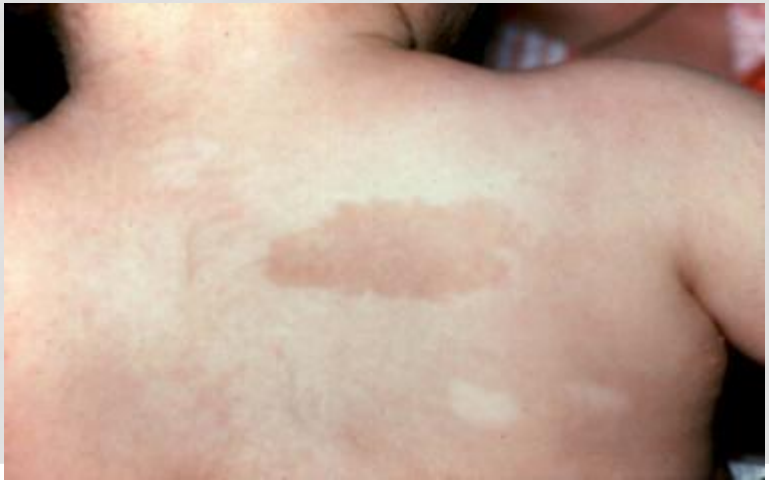
CLINICAL EXAMINATION

- Anthropometry including stature(Fanconi anemia, other congenital syndromes)
- Dysmorphic features; abnormal thumbs (Fanconi anemia)
- Pallor, jaundice(PNH, hepatitis, cirrhosis), lymphadenopathy(infection, lymphoproliferative disorder, HIV disease), edema
- Signs of congestive heart failure

Fanconi Anemia

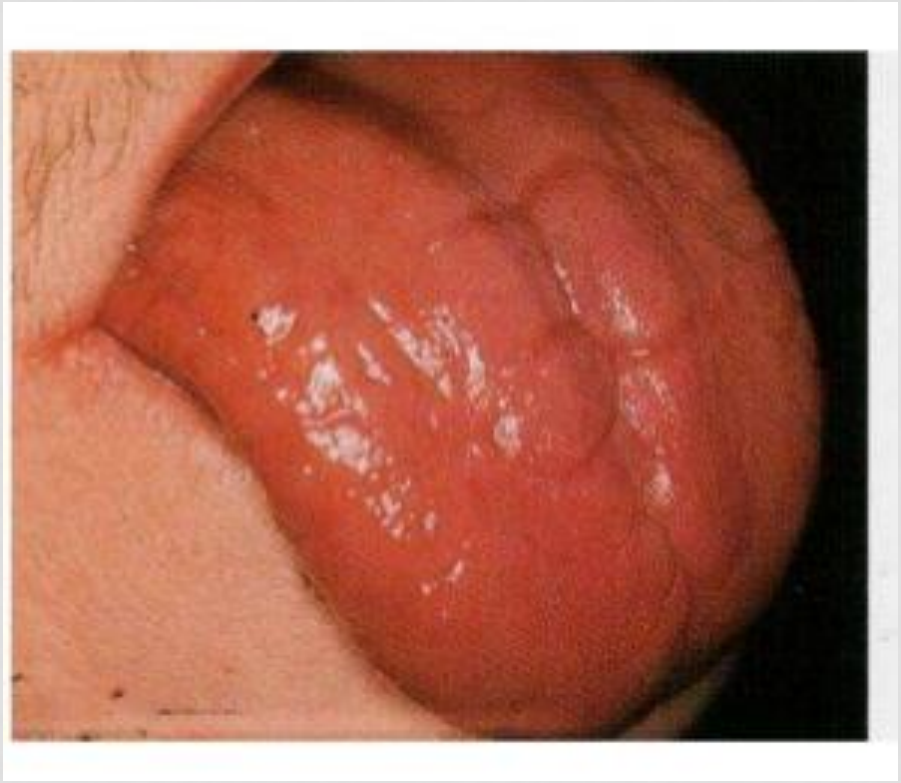






CLINICAL EXAMINATION

- Stomatitis, cheilitis (neutropenia, vitamin B12 deficiency)
- Nail dystrophy (dyskeratosis congenita), leukoplakia, skin pigmentation
- Oral candidiasis, pharyngeal exudates (neutropenia, herpes family virus infections)
- Gum hypertrophy



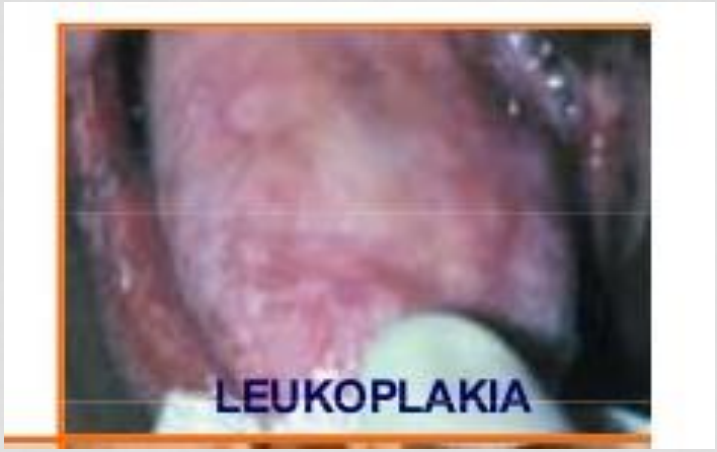
Vitamin B 12 (cobalamin)

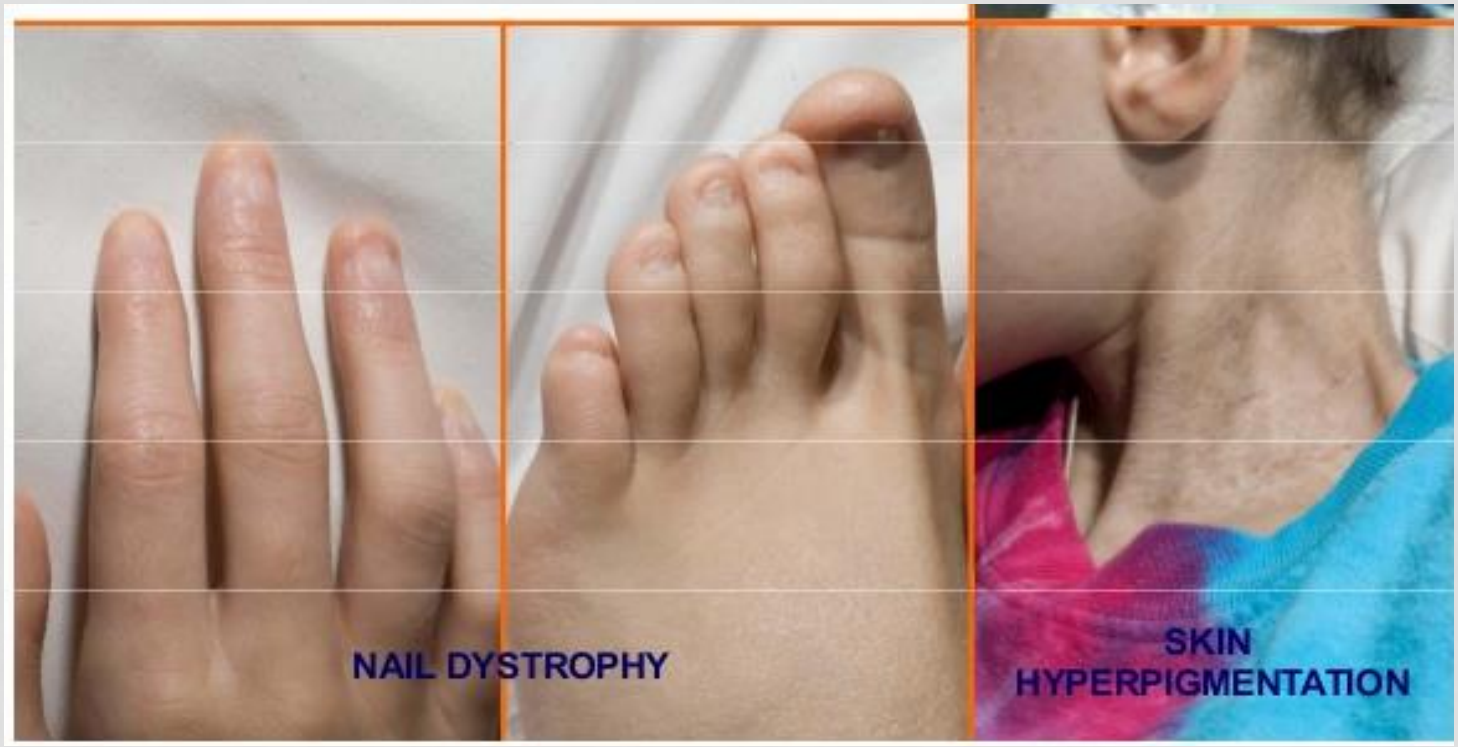
Common initial sign of B 12 deficiency:

The red sore tongue with atrophy of the papillae is often present in pernicious anemia

Angular stomatitis is also present

Dyskeratosis Congenita





CLINICAL EXAMINATION

- Petechiae, purpura, hyperpigmentation, café au lait(Fanconi anemia)
- Hepatosplenomegaly
- Joint swelling
- Weight loss or anorexia are harbingers of underlying infection and malignancy
- Widespread bone pain and loss of height suggest myeloma

INVESTIGATIONS

- CBC and examination of peripheral blood film
- Serum reticulocyte count
- Serum liver function test—evaluate hepatitis
- Hepatic serology
- Serum coagulation profile, bleeding time, fibrinogen and D-dimer
- Serum direct antiglobulin test
- Serum B12 and folate---megaloblastic anemia
- Serum HIV and nucleic acid testing, EBV

RETICULOCYTE COUNT

- Absolute reticulocyte count (ARC) is a calculated index derived from the product of reticulocyte count percentage and RBC count (Normal; Male: 4.32-5.72 million/cmm, Female: 3.90-5.03 million/cmm)
- ARC is a marker of red cell production by bone marrow

- It plays important role in establishing the cause of pancytopenia and helps in distinguishing between hypoproliferative and hyperproliferative anaemias
- Normal range of absolute reticulocyte count is 50,000-100,000/cmm.

RETICULOCYTE COUNT

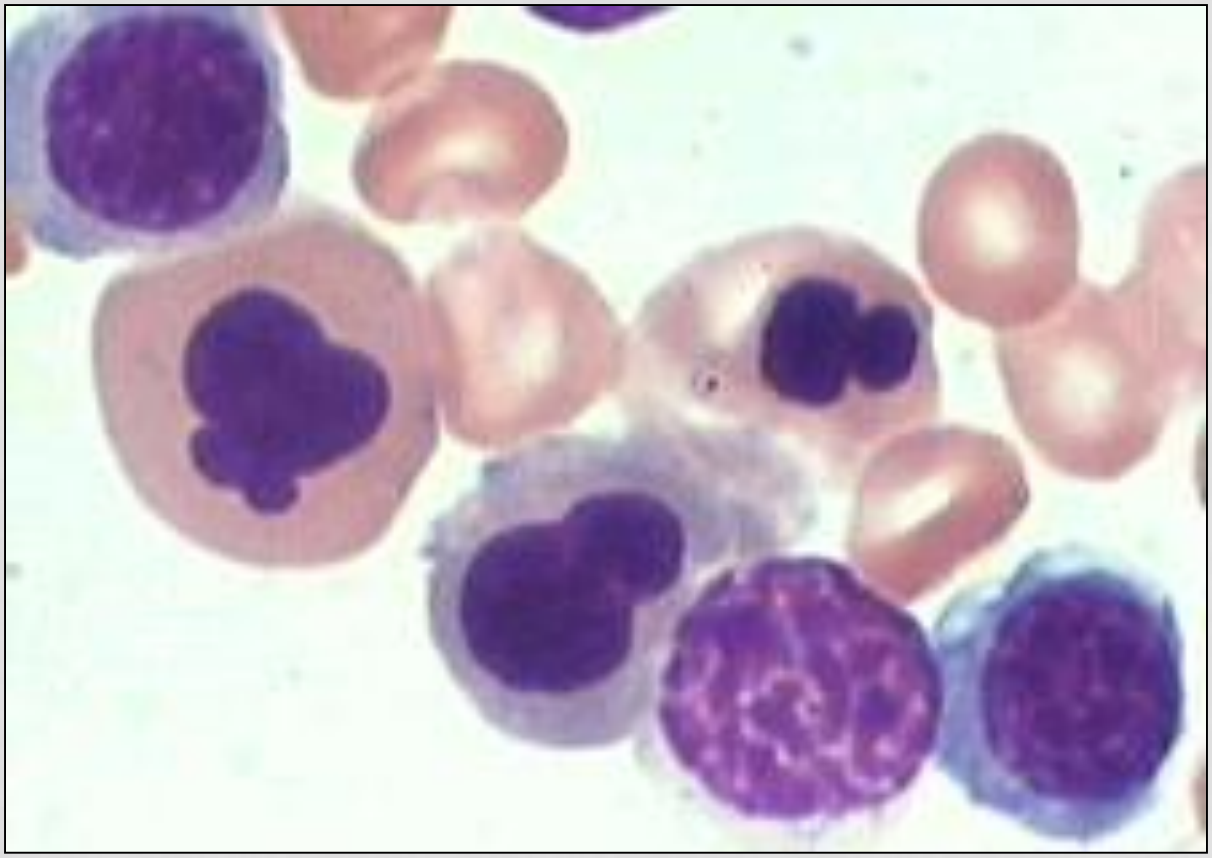
- All cases of pancytopenia with very low ARC (< 25,000/cmm) should be examined by bone marrow aspiration for aplastic anaemia

- All cases of pancytopenia with high ARC (> 100,000/cmm) should also be evaluated by bone marrow aspiration
- Pancytopenia with ARC 25,000-50,000/ cmm should initially be evaluated with serum B12, folate and ferritin assays

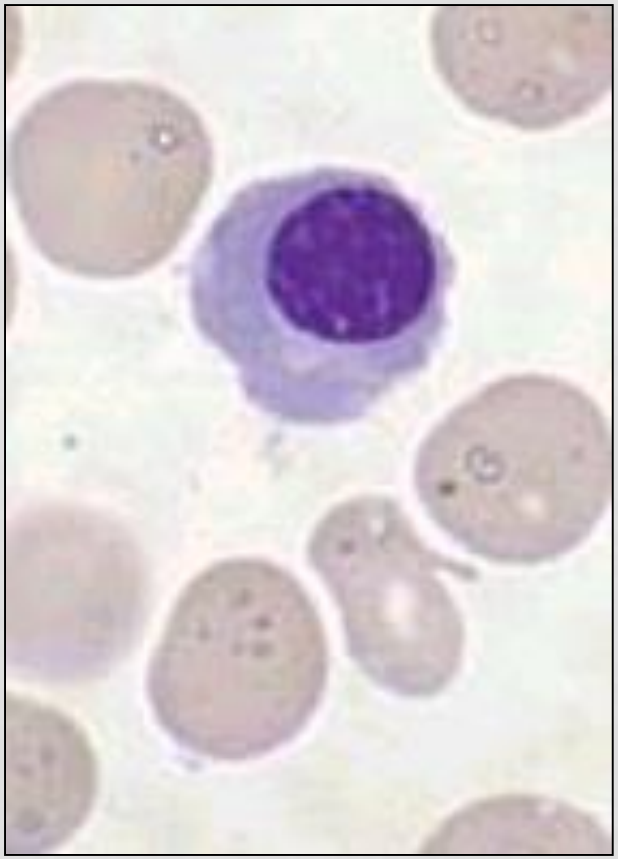
PERIPHERAL SMEAR

- Red cell morphology
- Normocytic normochromic with no anisopoikilocytosis, no NRC, reticulocytopenia---aplastic anemia
- Macroovalocytes with Howell Jolly bodies-megaloblastic anemia
- Tear drop cells, HJ bodies and basophilic stipping--MDS

DYSPLASTIC ERYTHROID MATURATION (DYSERYTHROPOIESIS)



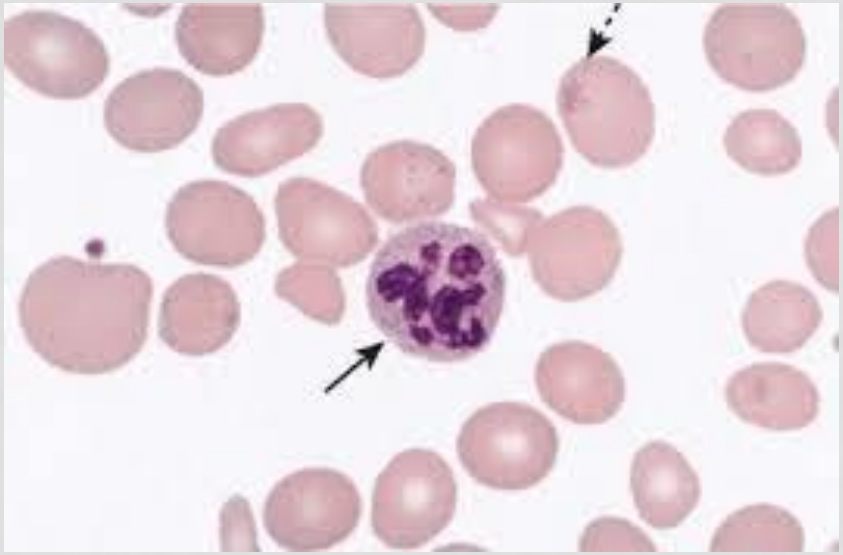
Dyserythropoiesis



Normal

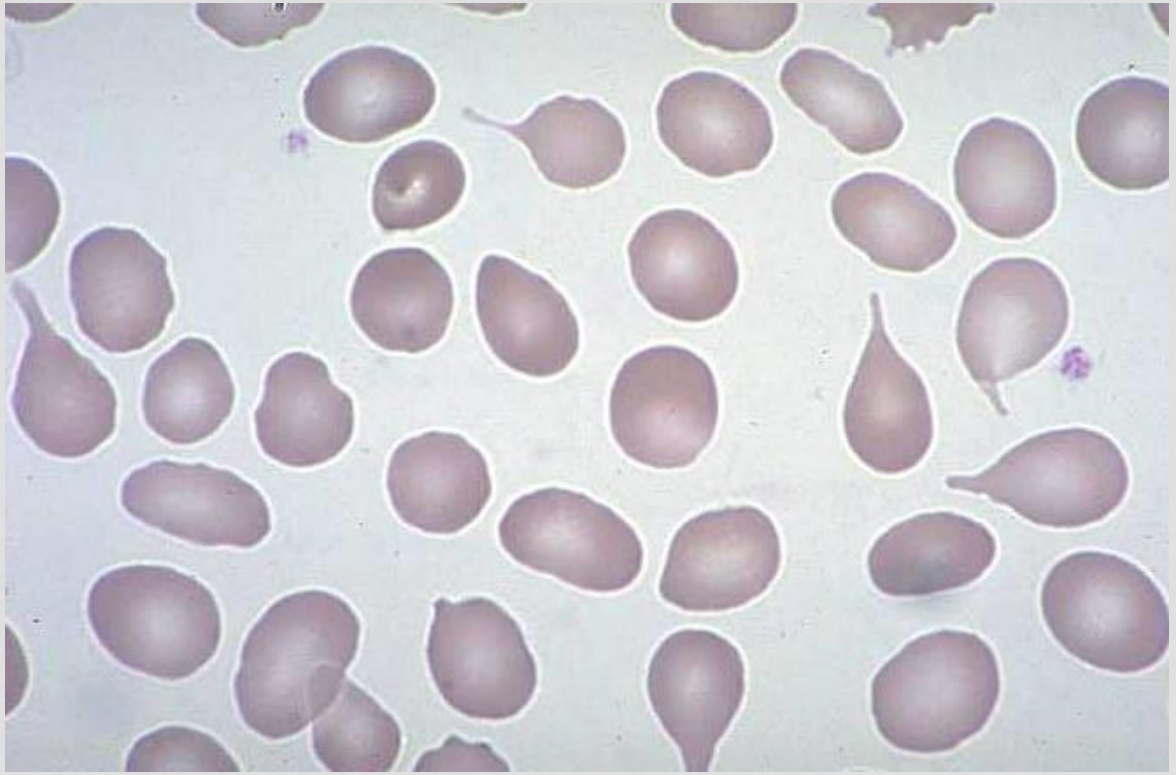
PERIPHERAL SMEAR

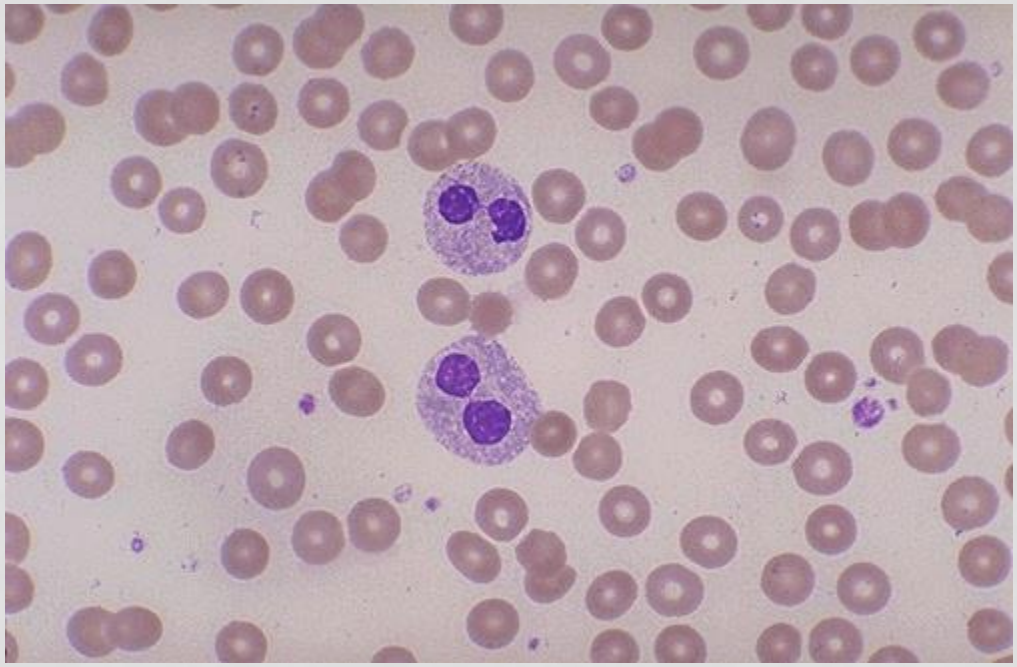
- **WBCs**
- Leucopenia(mostly mature80%)—aplastic anemia
- Neutrophils present in increased number with toxic granules, shift to the left-infections
- Basophilic stippling, hypersegmented neutrophils—megaloblastic anemia
- Blasts-leukemia
- Hypogranular neutrophils, pseudo Pelger Huet anomaly--MDS



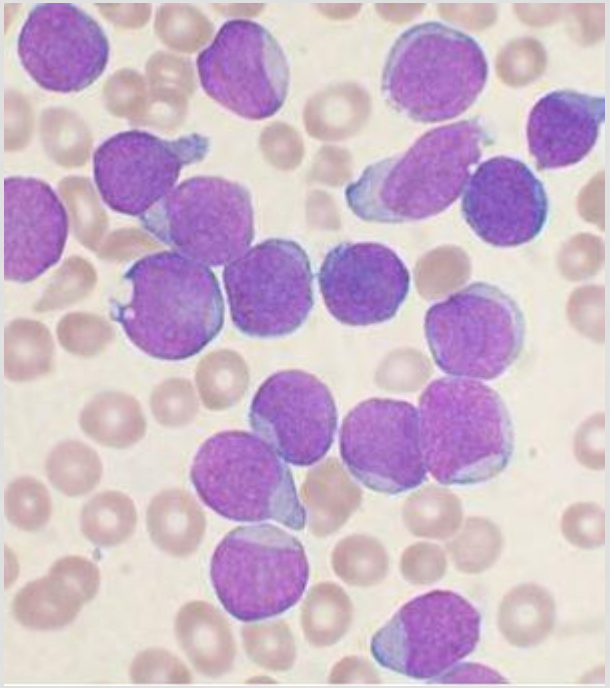
Hypersegmented neutrophils

Tear drops





Pelger Huet anomaly



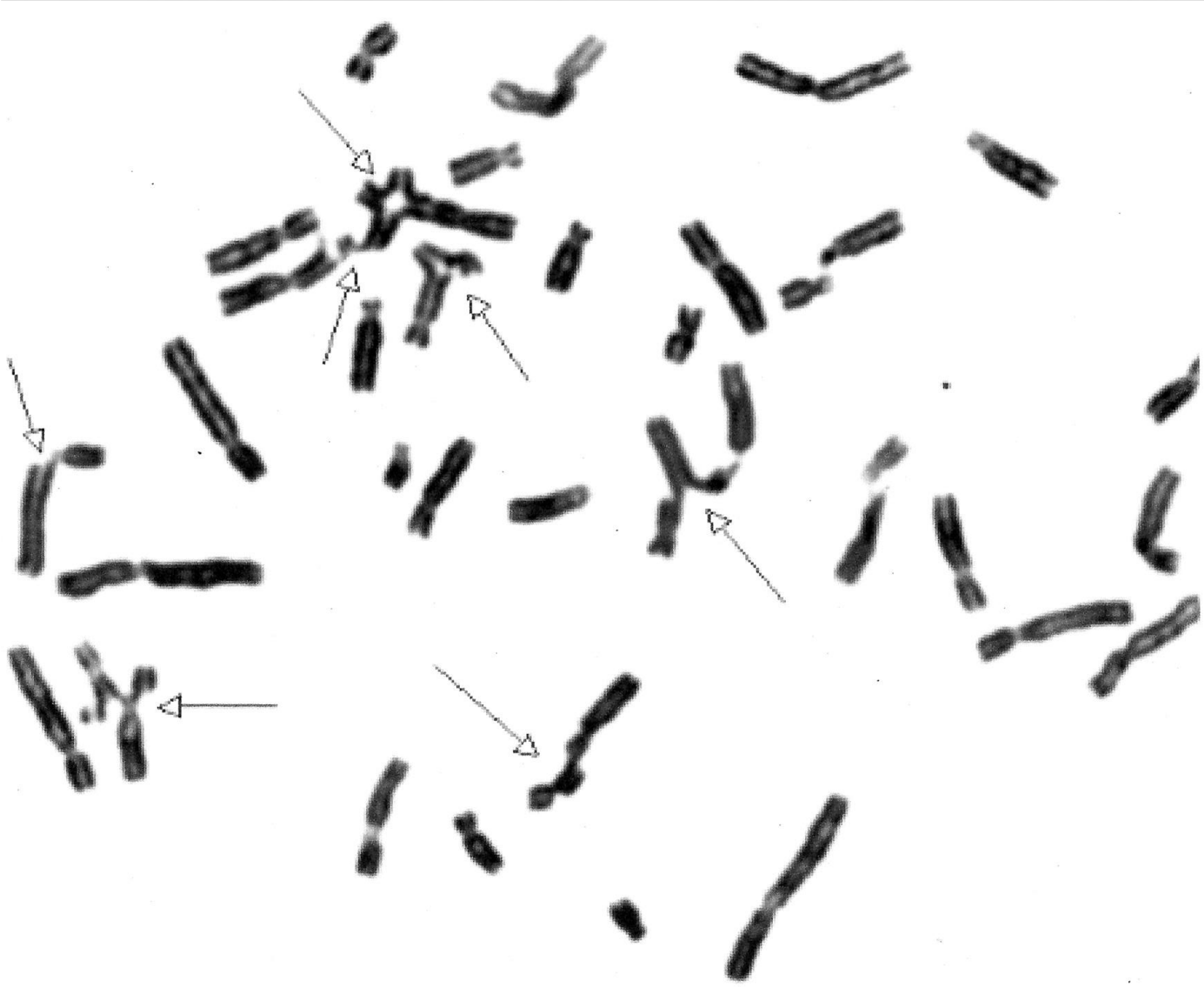
PERIPHERAL SMEAR

- **Platelets**
- Normal count—rule out aplastic anemia

- Giant platelets-MDS/hypersplenism

INVESTIGATIONS

- **Specific testing pinpoints diagnosis in the following conditions;**
- Fanconi anemia; diepoxybutane (DEB) test for chromosomal breakage in peripheral blood lymphocytes
- Lymphoproliferative disorders: immunophenotyping, cytogenetics, lymph node biopsy



INVESTIGATIONS

- Multiple myeloma: immunoelectrophoresis
- Paroxysmal nocturnal hemoglobinuria (PNH): peripheral blood immunophenotyping for deficiency of phosphatidylinositol-glycan-linked molecules on peripheral blood cells (CD55, CD59)

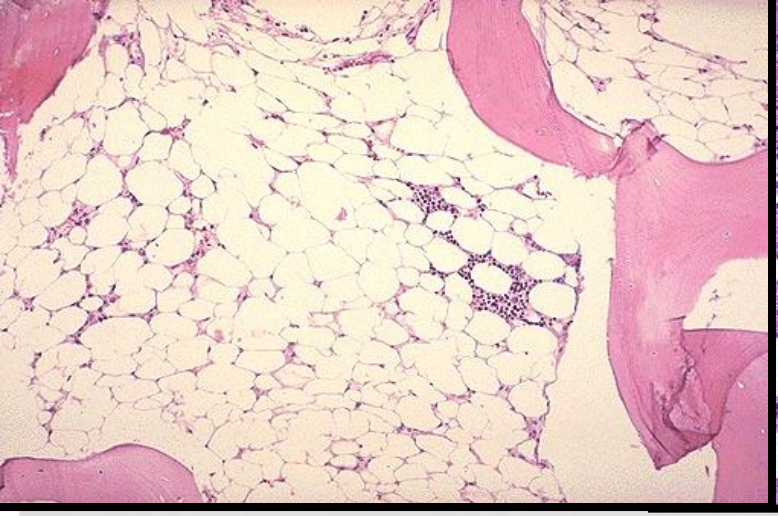
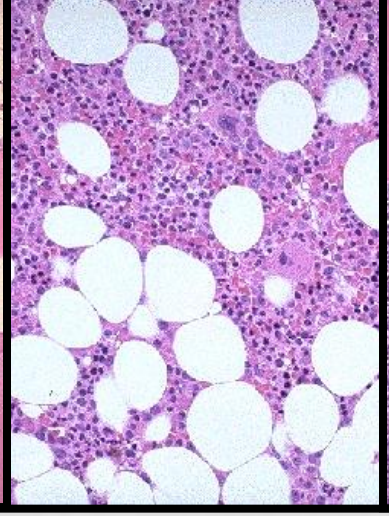
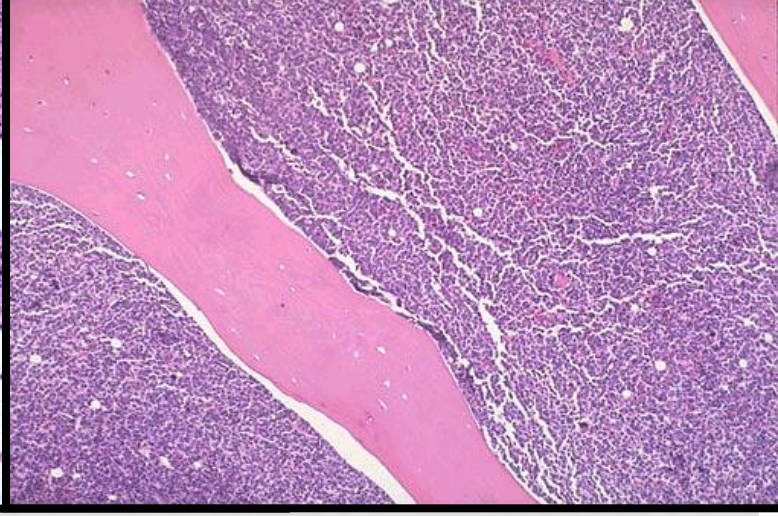
INVESTIGATIONS

- CMV infection: serum IgM and IgG
- Epstein-Barr: serum monospot, viral capsid antigen (VCA), and Epstein-Barr nuclear antibody (EBNA)
- Leishmaniasis and other rare infections; blood and bone marrow culture, serum ELISA

- Rare genetic and metabolic disease: leukocyte glucocerebrosides
- Serum PSA in suspect cases of prostate malignancy

BONE MARROW EXAMINATION

- Almost always indicated in cases of pancytopenia unless cause is otherwise apparent
- Consists of both an aspirate and a trephine biopsy
- The differential diagnosis is based on the; bone marrow cellularity
- Reduce indicates decreased production of blood cells
- Normal/increase indicates ineffective production or increased destruction or sequestration of blood cells

hypocellular

aplastic anemia

hypercellular

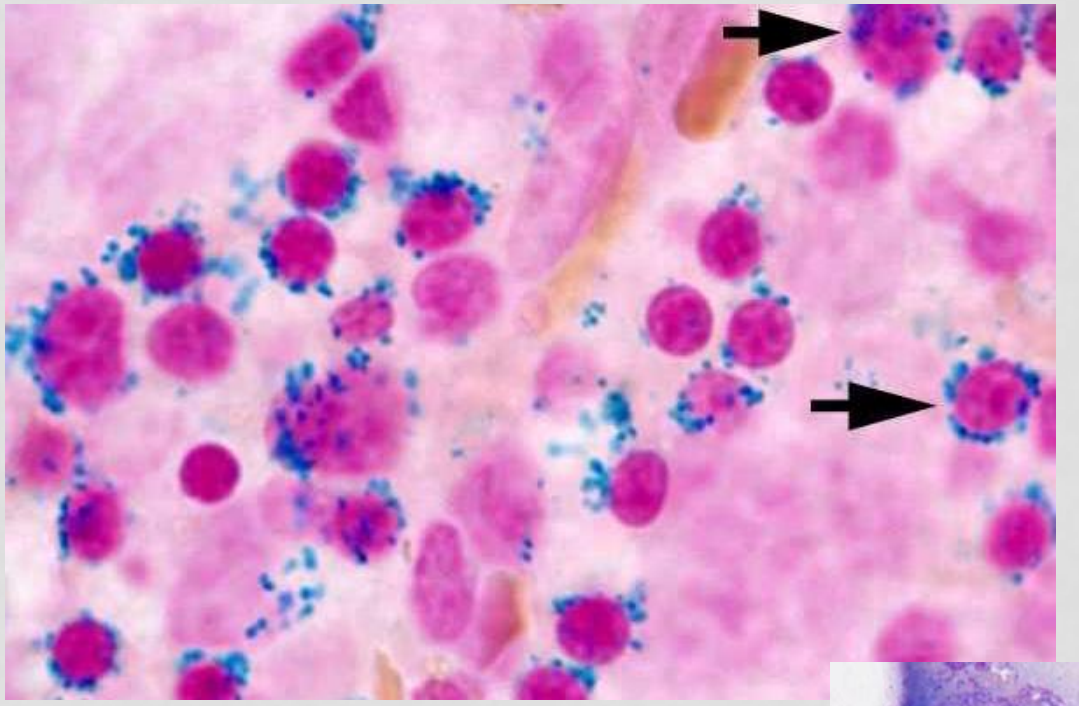
destruction
hypersplenism
MDS
infiltration
B12 def
myelofibrosis

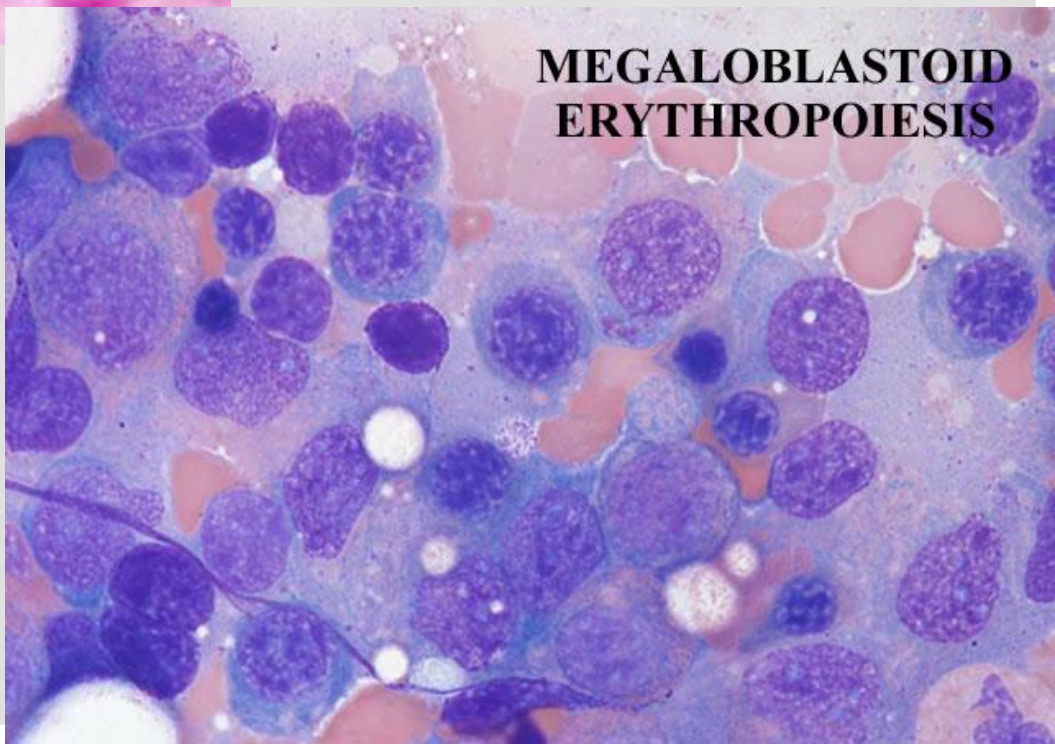
BONE MARROW EXAMINATION

- Examination; cytology—megaloblastic change, dysplastic changes, abnormal cell infiltrates, hemophagocytosis, and infection
- Immunophenotyping—acute and chronic leukemias, lymphoproliferative disorders
- Cytogenetics – myelodysplasia, acute and chronic leukemias, lymphoproliferative disorders

BONE MARROW EXAMINATION

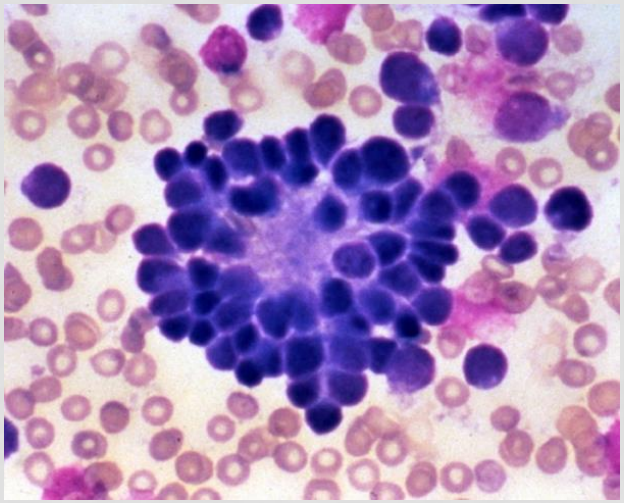
- Biopsy
- Erythroid hyperplasia with megablastosis---megaloblastic anemia
- Trilineage dysplasis with ringed sideroblasts on pearl's stain---MDS

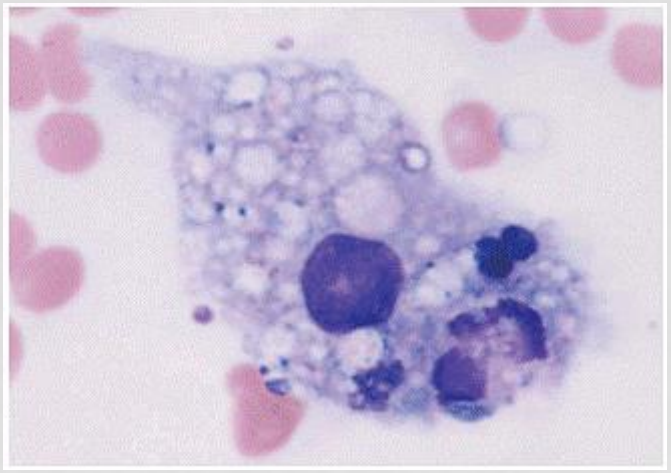


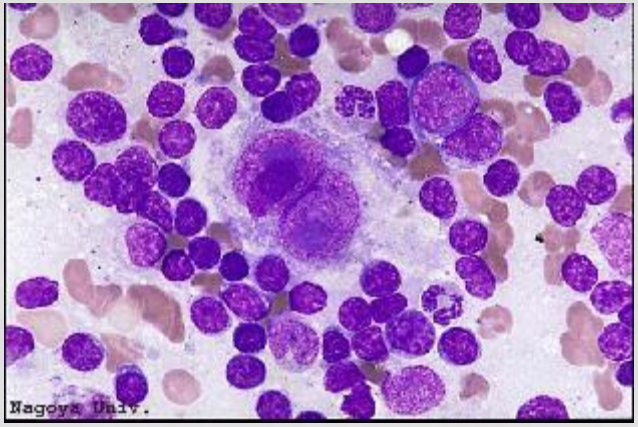

MEGALOBLASTOID
ERYTHROPOIESIS

BONE MARROW EXAMINATION

- Infiltration by RS cells---hodgkin lymphoma
- Infiltration with malignant cells---metastasis
- In PNH& Fanconi anemia---early stage will show hypercellular normal appearing marrow



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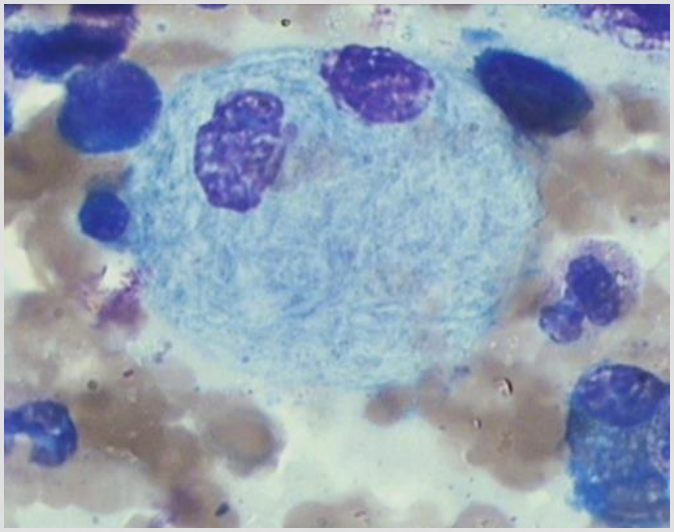


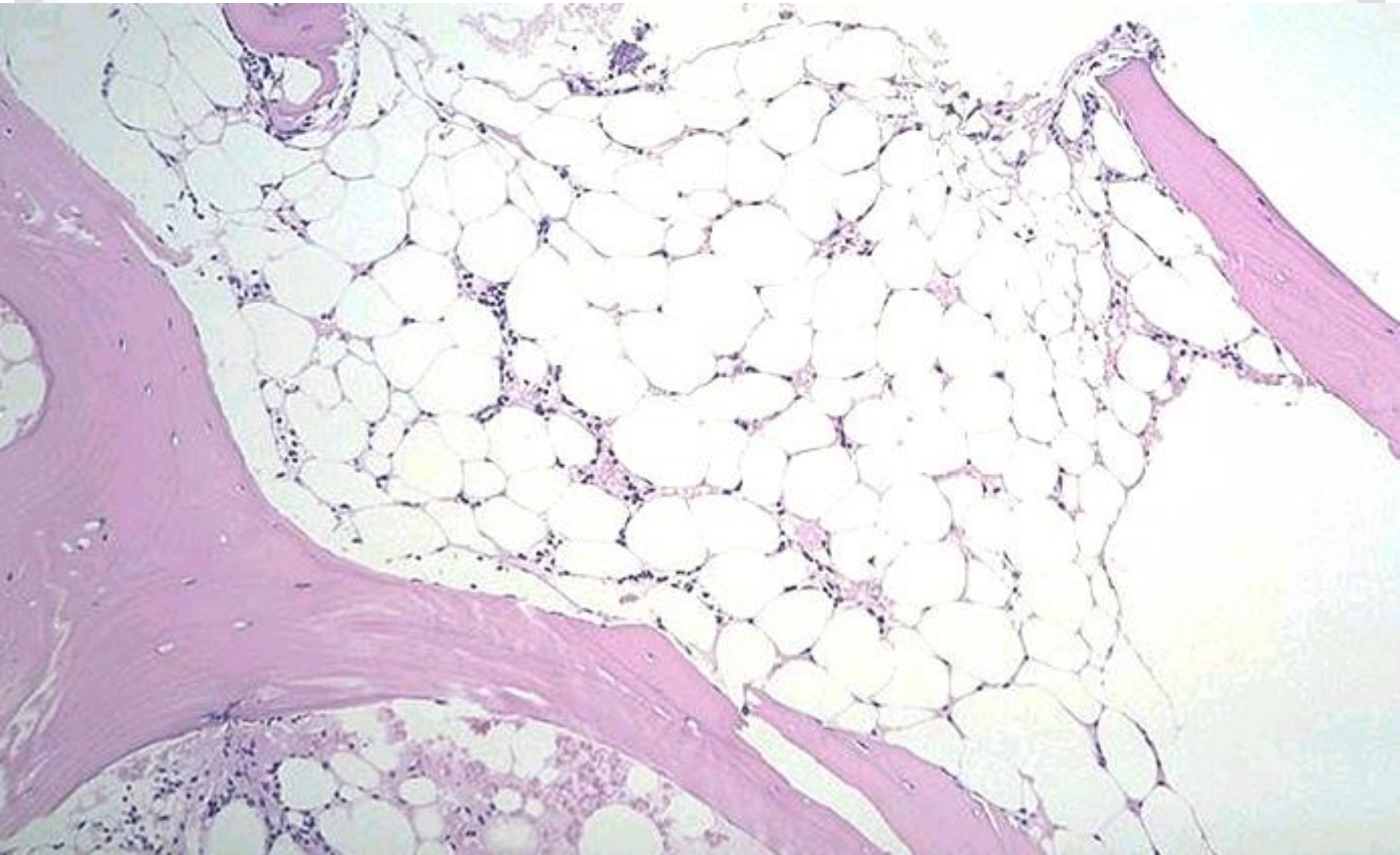
BONE MARROW EXAMINATION

- Aspiration
- Empty particles, markedly hypocellular, only scattered mature lymphocytes&sometimes excess plasma cells- aplastic anemia
- Pockets of cellularity with widespread hypocellularity-evolving aplastic anemia

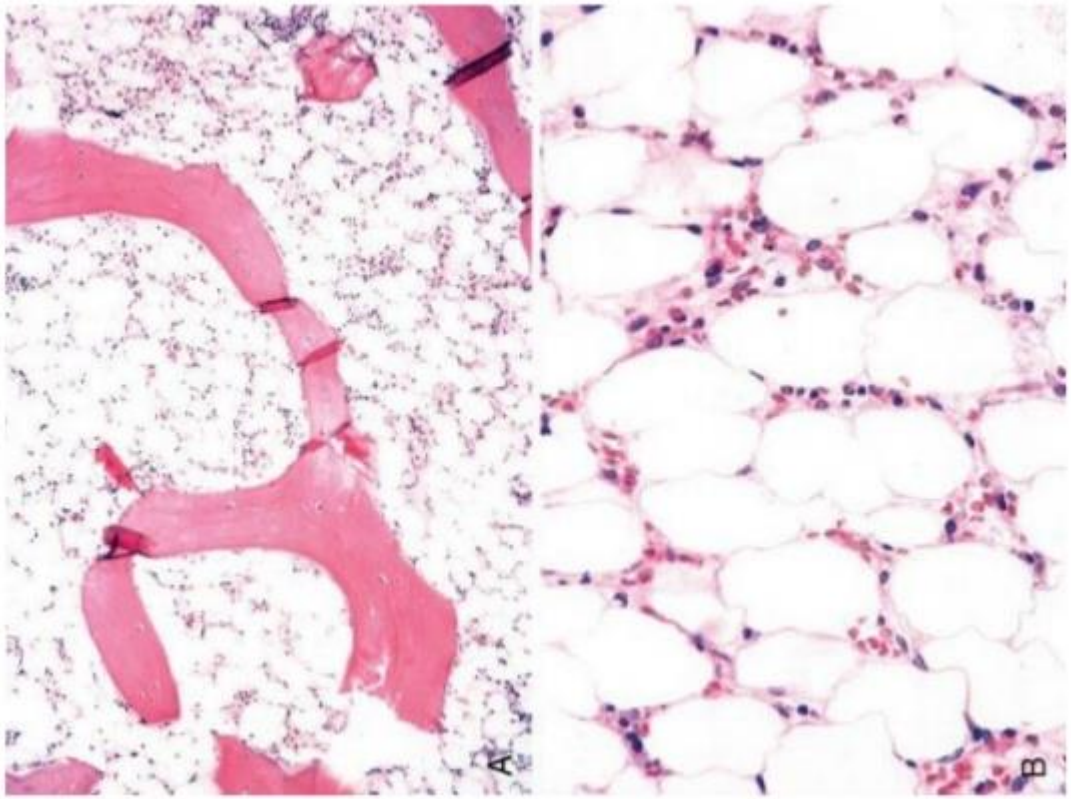
BONE MARROW EXAMINATION

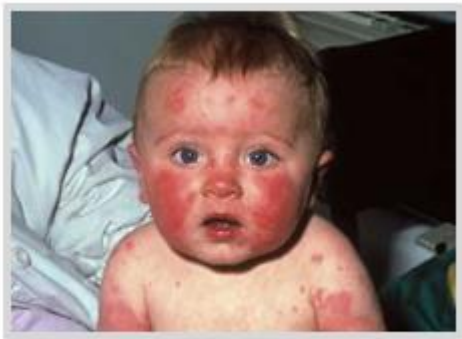
- Hypocellular with BM blasts (>20%)-hypoplastic leukemia
- Hypocellular BM with dysplastic megakaryocytes—hypoplastic MDS(diseases of haematopoietic stem cells, characterized by disturbance of differentiation and maturation, and by changes in the bone marrow stroma)
- Scattered proerythroblasts with large nuclear inclusions in hypocellular BM--parvovirus

APLASTIC ANEMIA

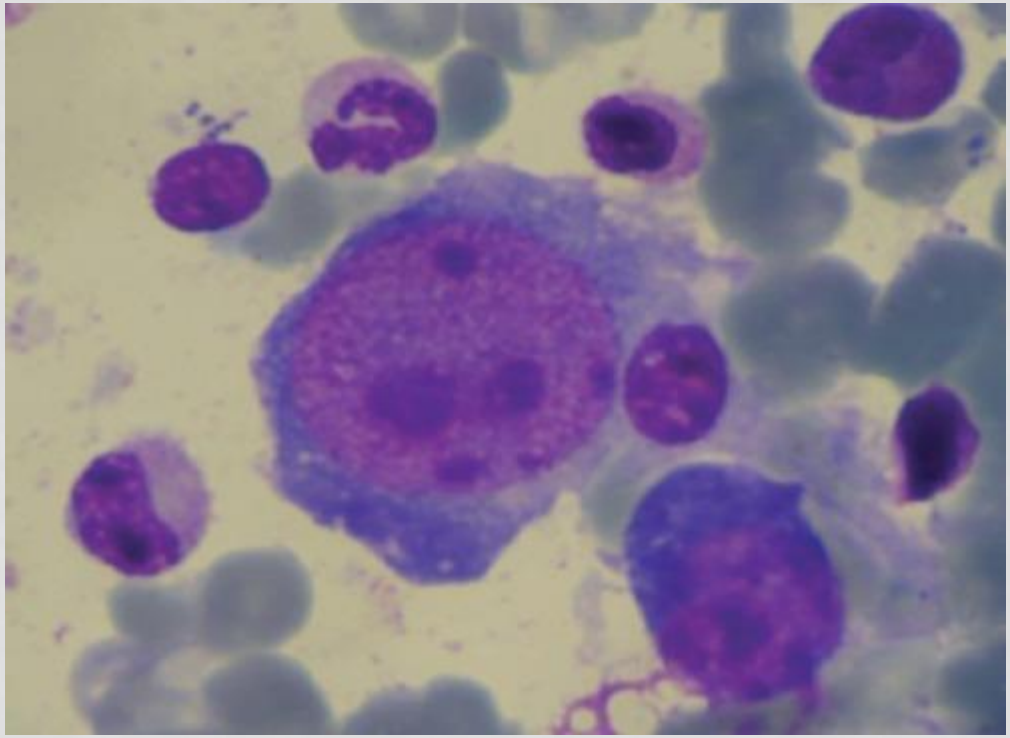


Morphology





Baby with the typical "slapped-cheek" rash, which is characteristic of fifth disease.



Giant proerythroblasts with nuclear inclusions

THANK YOU FOR YOUR ATTENTION