Myelodysplastic Syndromes

MDS

- Refractory cytopenias with unilineage dysplasia: anemia (RA), refractory neutropenia (RN), refractory thrombocytopenia (RT)
- Refractory anemia with ring-sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with excess blasts (RAEB)
- Myelodysplastic syndrome, unclassified
- Myelodysplastic syndrome with isolated del (5q)

Introduction

General:

-Stem cell disorder

-Dysplasia

-Ineffective hematopoiesis

-Blasts <20% in blood and BM

- Median age: 70 y/o

- Incidence: 3-5/100,000

Introduction

- **New subtypes:**
  - Refractory neutropenia (RN), refractory thrombocytopenia (RT)
  - Childhood MDS

Clinical Features

- **Related to:**
  - Cytopenias
  - Anemia, most frequently
  - Neutropenia, thrombocytopenia
  - Organomegaly (infrequently observed)

Cytopenias in MDS

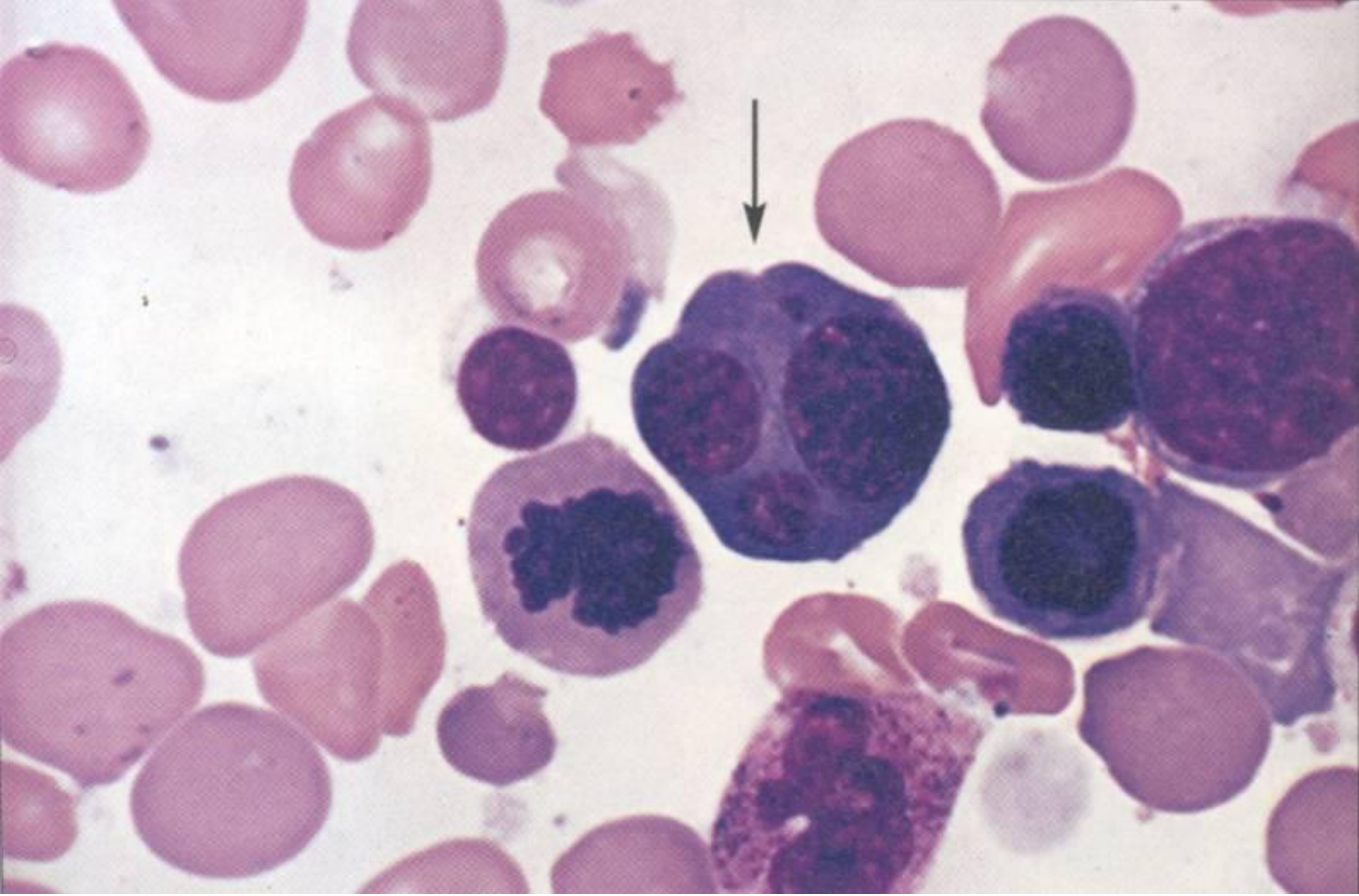
- Refractory cytopenias with unilineage dysplasia: anemia (RA), refractory neutropenia (RN), refractory thrombocytopenia (RT): 1-2 cell lines
- Refractory anemia with ring-sideroblasts (RARS): 1-2
- Refractory cytopenia with multilineage dysplasia (RCMD): 1-3
- Refractory anemia with excess blasts (RAEB): 1-3
- Myelodysplastic syndrome, unclassified: 0-3
- Myelodysplastic syndrome with isolated del (5q):1-2

Etiology

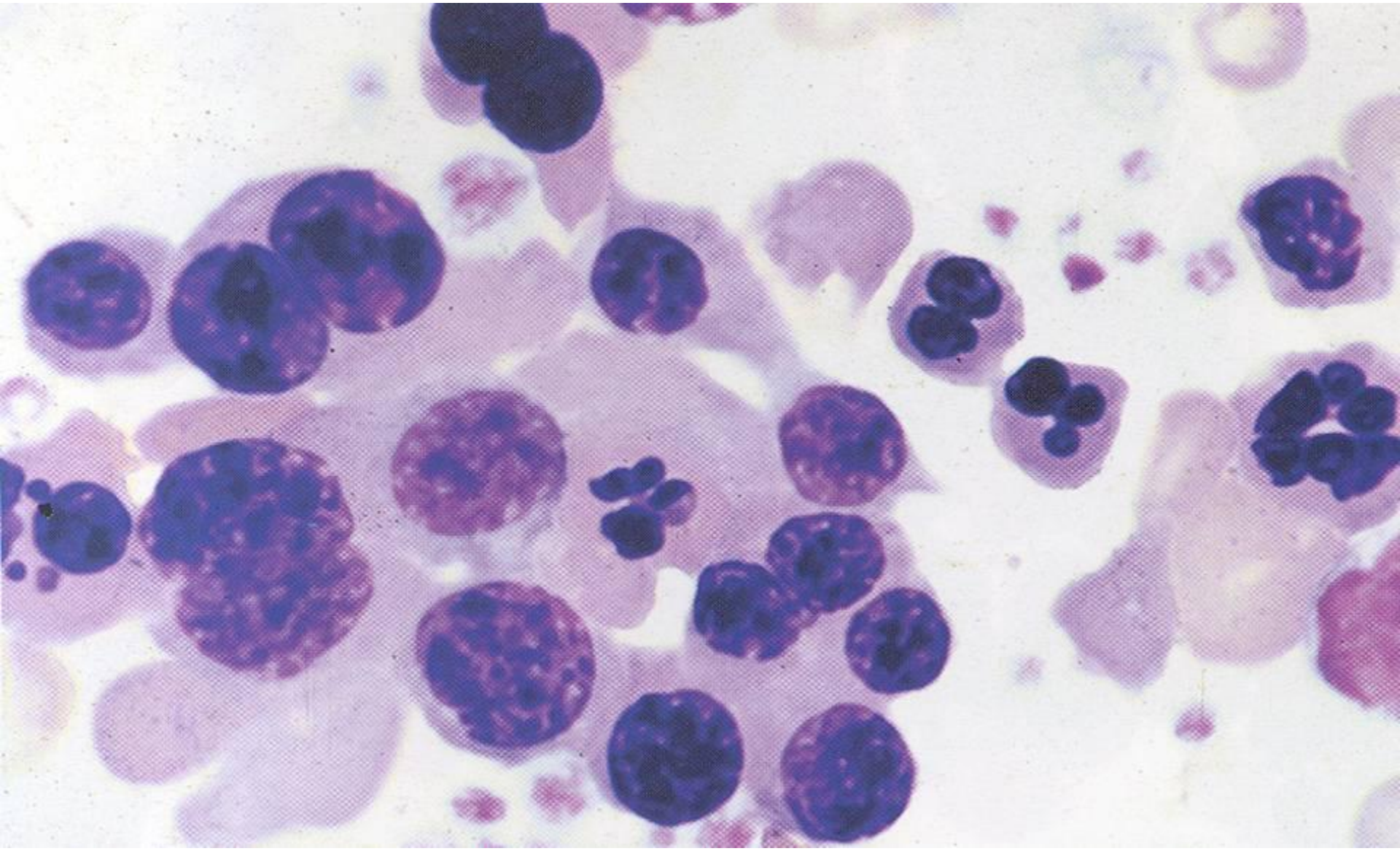
- Virus, benzene, cigarette smoking (2-fold increase), Fanconi's anemia
- Therapy related (t-MDS): esp. alkylating agents
- Most cases with unknown etiology

Morphology

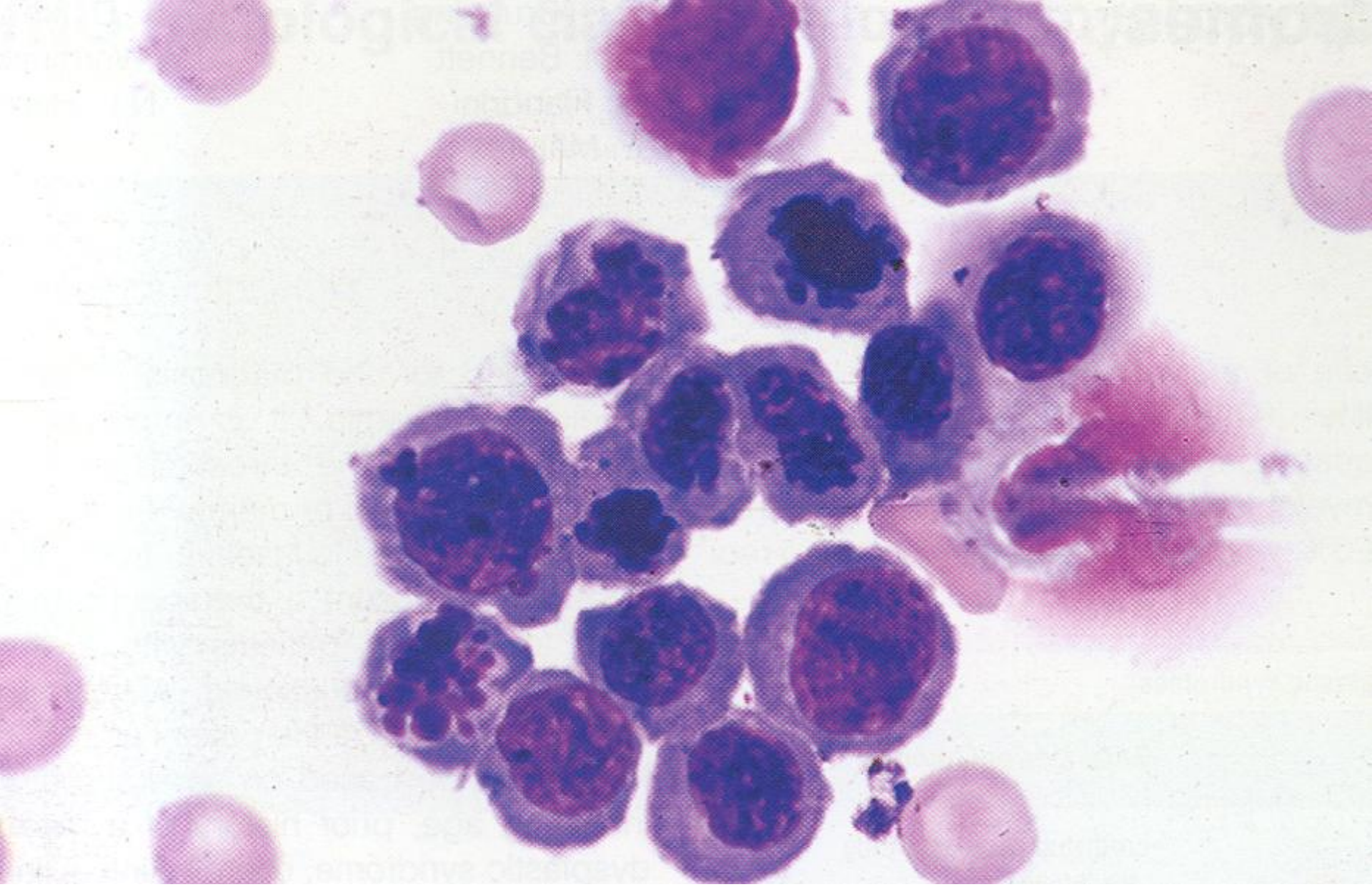
- Dyserythropoiesis
- Dysgranulopoiesis
- Megakaryocyte dysplasia
- BM: hypercellular (sometines normal, or hypocellular)
- BM bx may have abnormal localization of immature precursors (ALIP): 5-8 immature cell cluster, 3 or more ALIPs per section-> (+); recheck smear and BM, note in report.



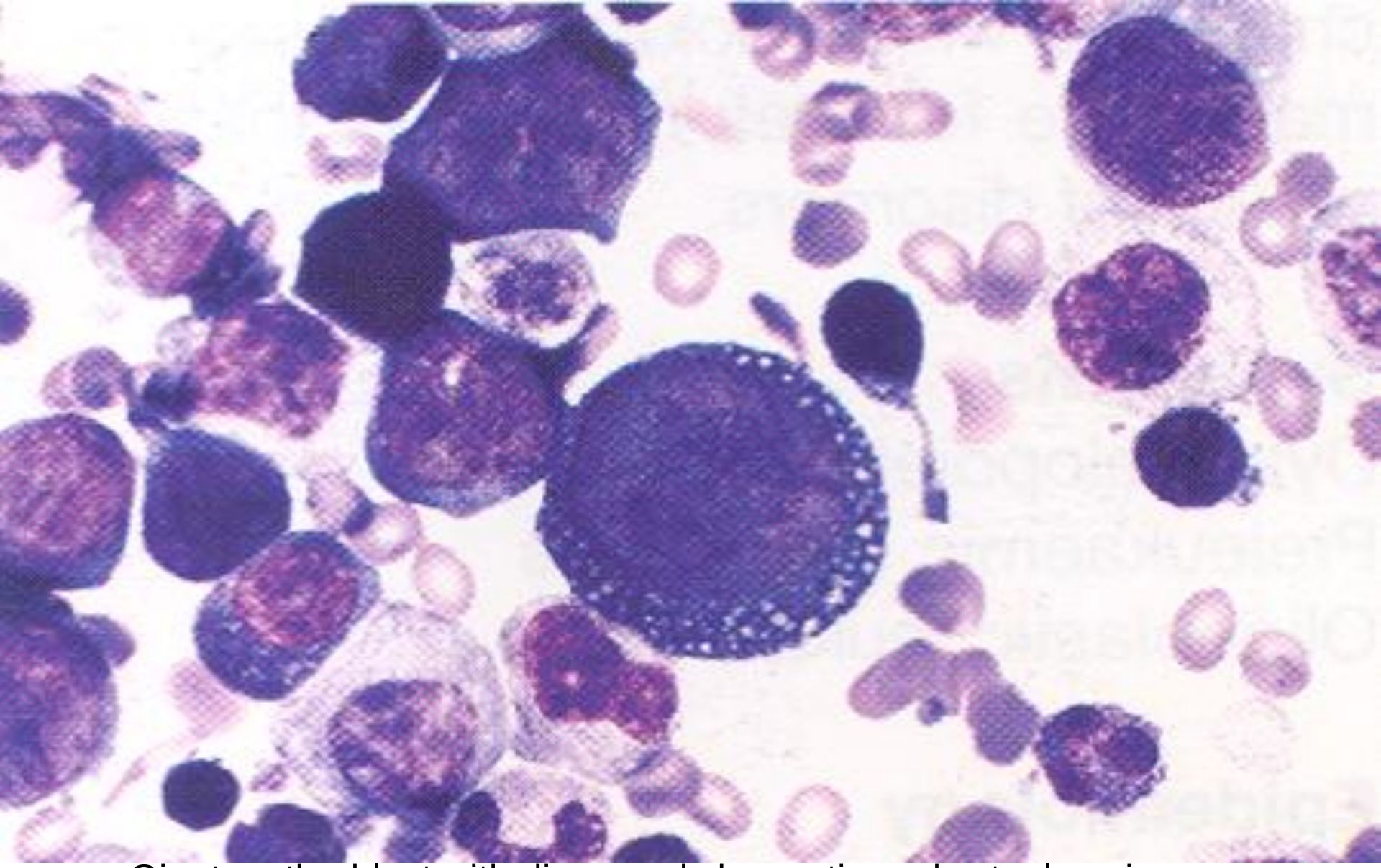
Multinucleated megaloblastoid erythroid precursors,
Bone marrow aspirate



Dyserythropoiesis, Bone marrow aspirate

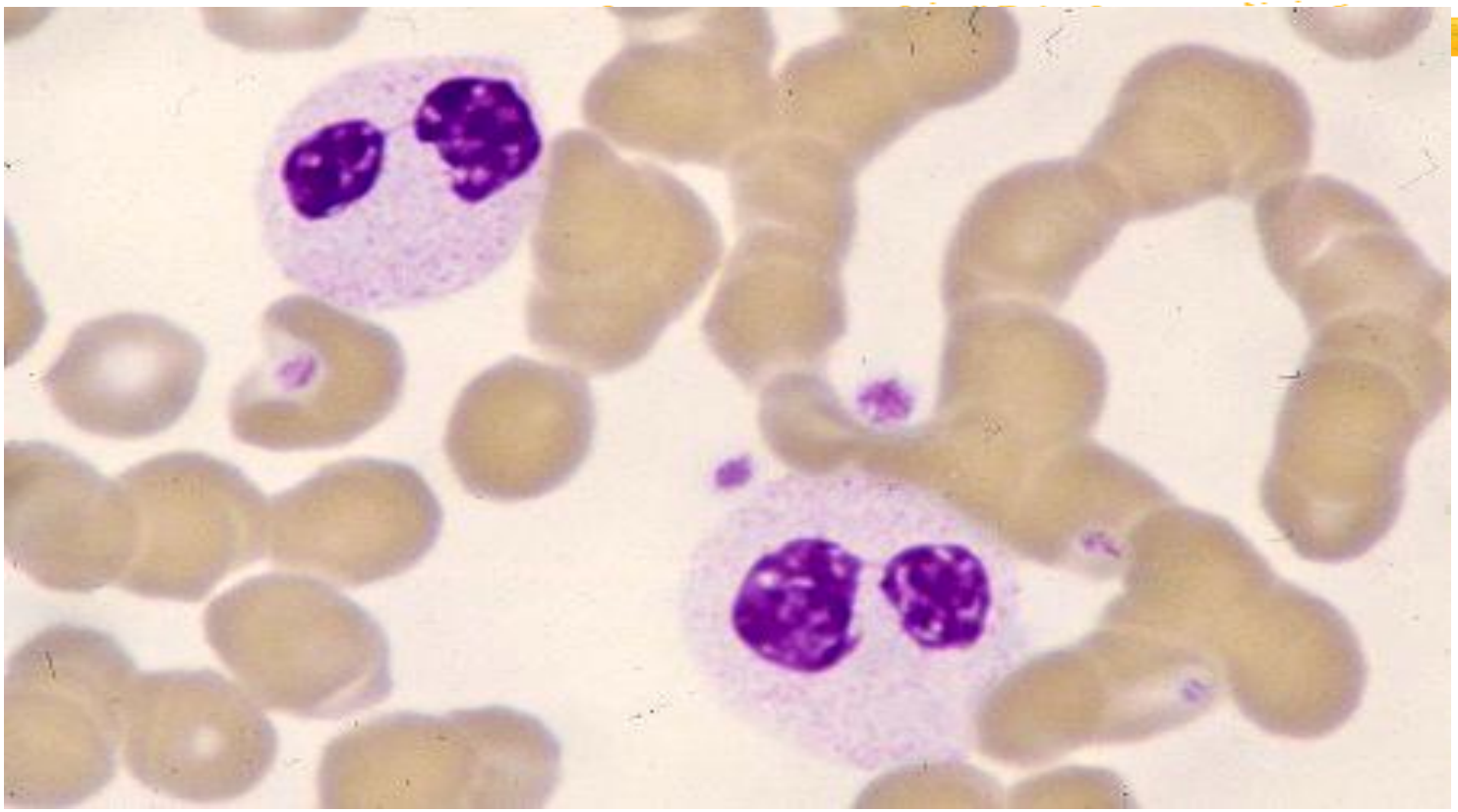


Dyserythropoiesis, Bone marrow aspirate

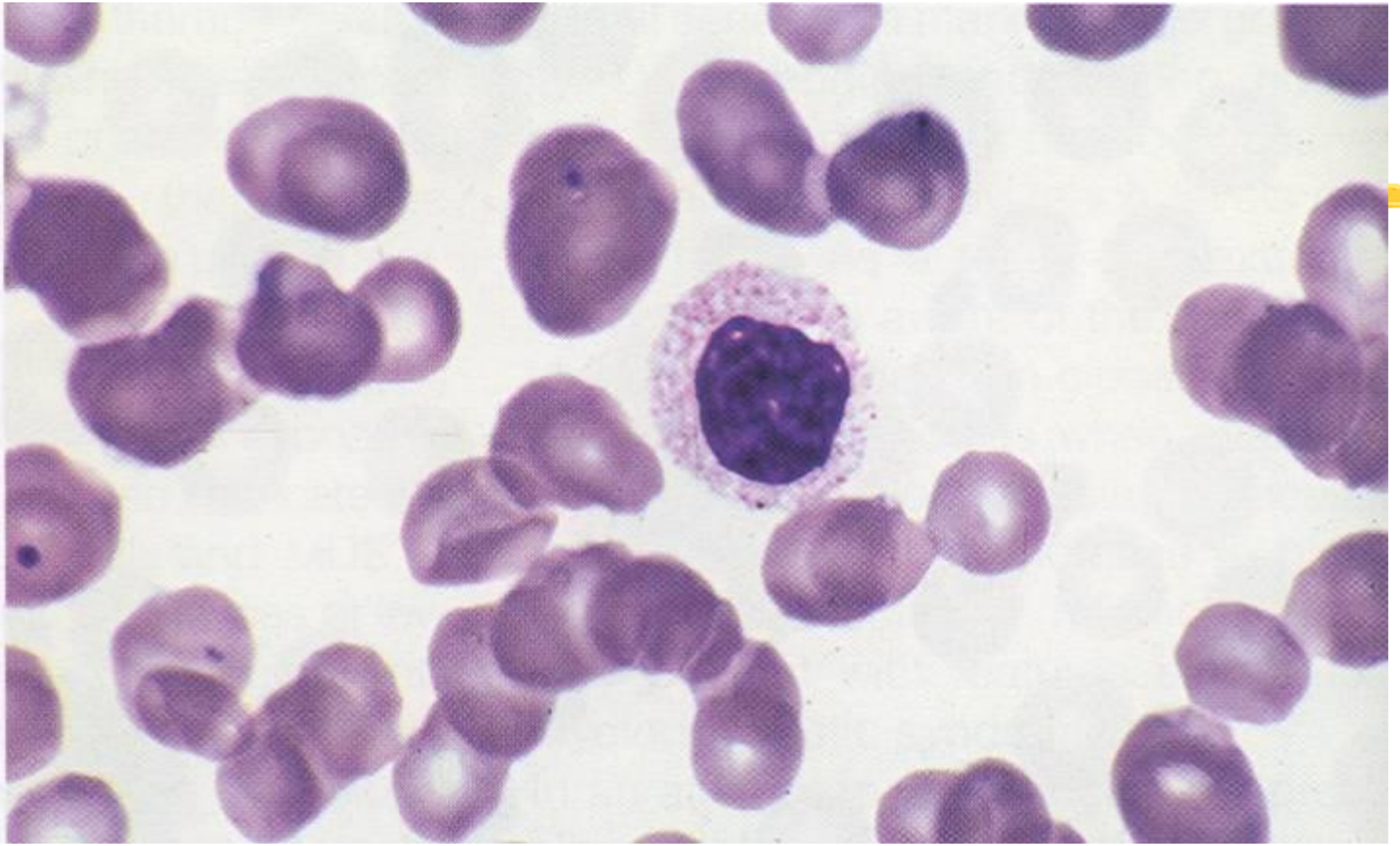


Giant erythroblast with dispersed chromatin and cytoplasmic vacuoles, Bone marrow smear.

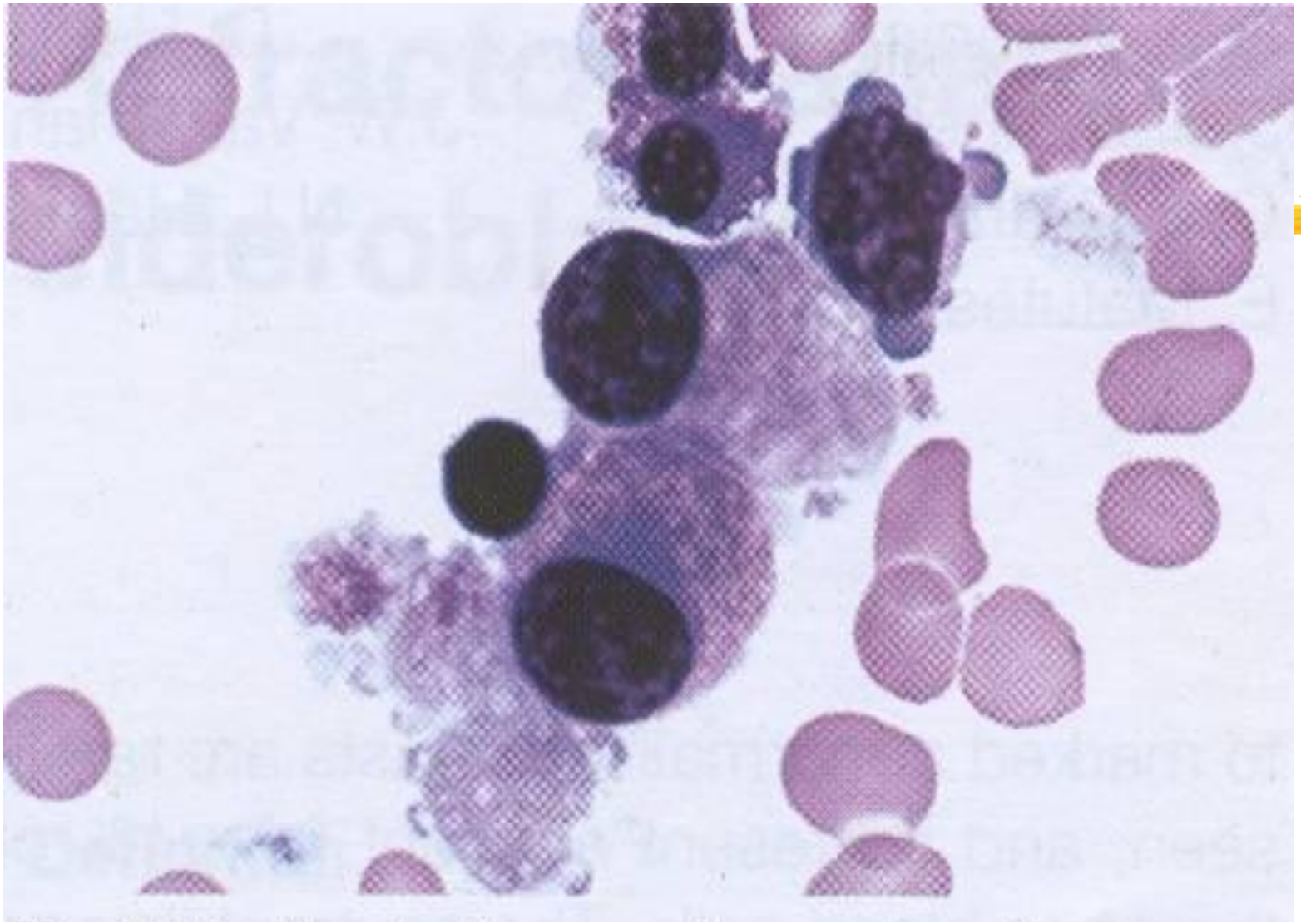
Dysgranulopoiesis



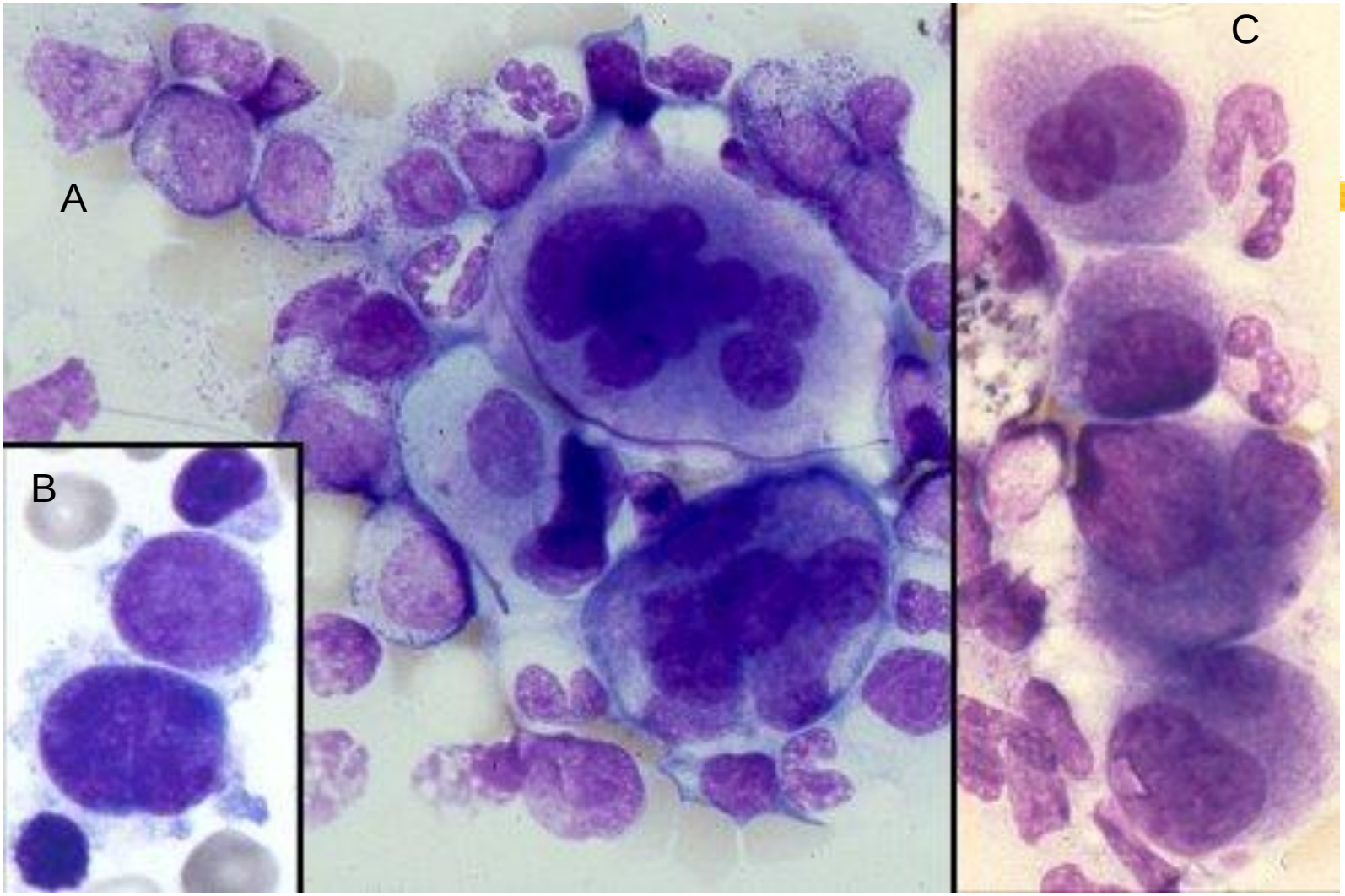
Circulating pseudo-Pelger-Huet neutrophils, with hypogranular cytoplasm, bilobed 'spectacle' nuclei, Blood smear



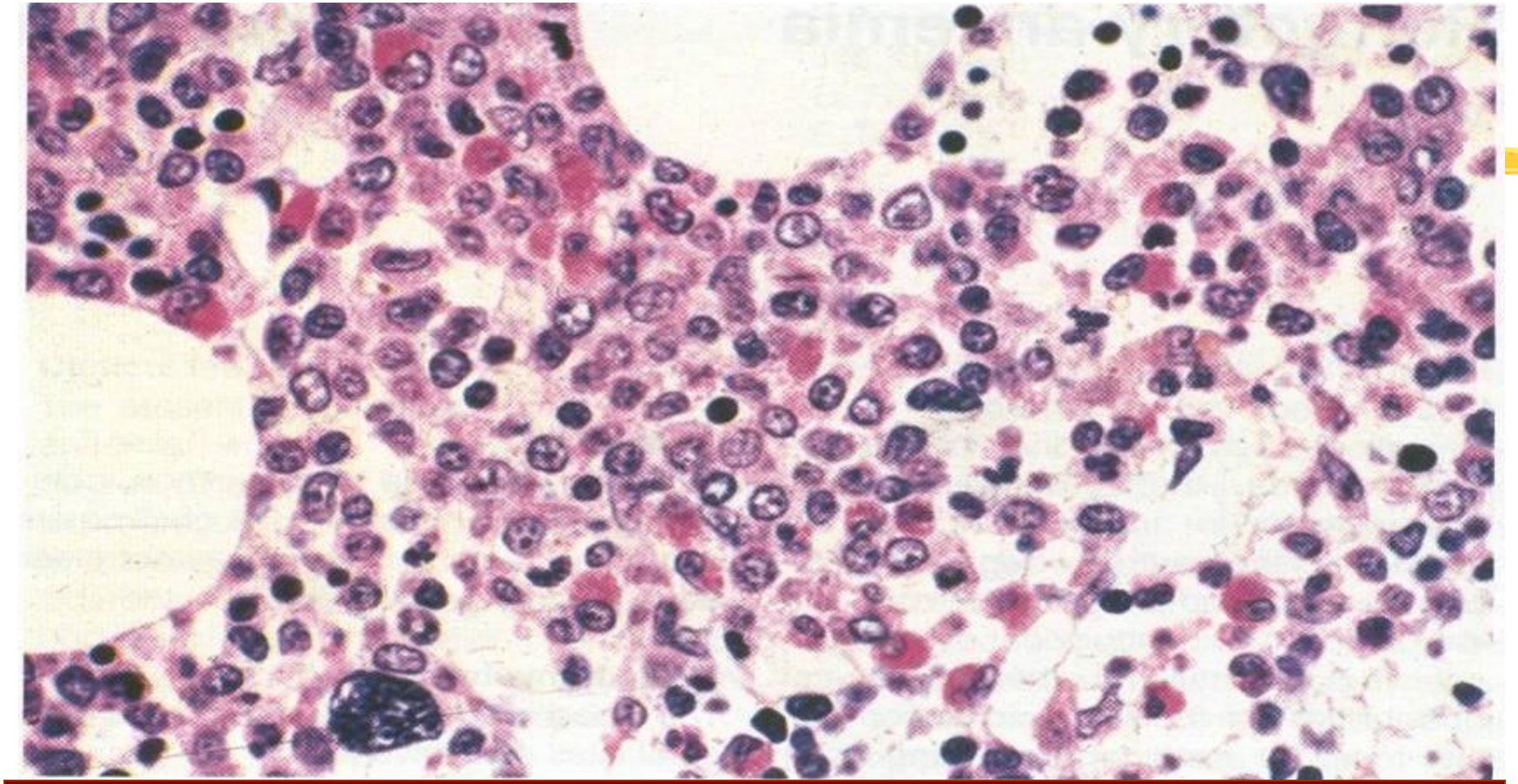
Neutrophil with non-lobulated nucleus, Blood smear



Dysplastic megakaryocytes, Bone marrow aspirate



A. Dysplastic megakaryocytes.
B. Micromegakaryocytes with dense nuclear chromatin.
C. Immature megakaryocytes with nuclear lobe separation.

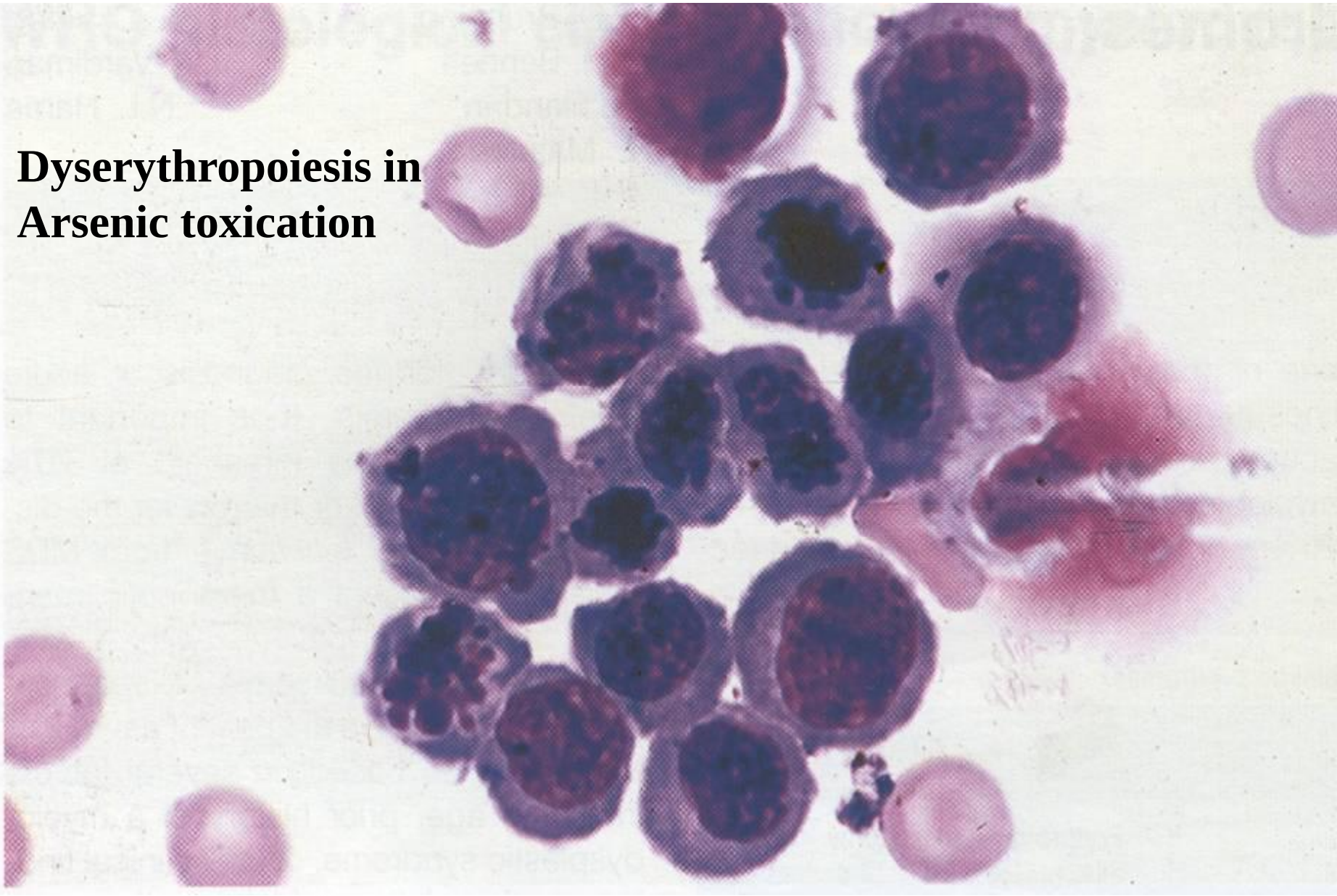


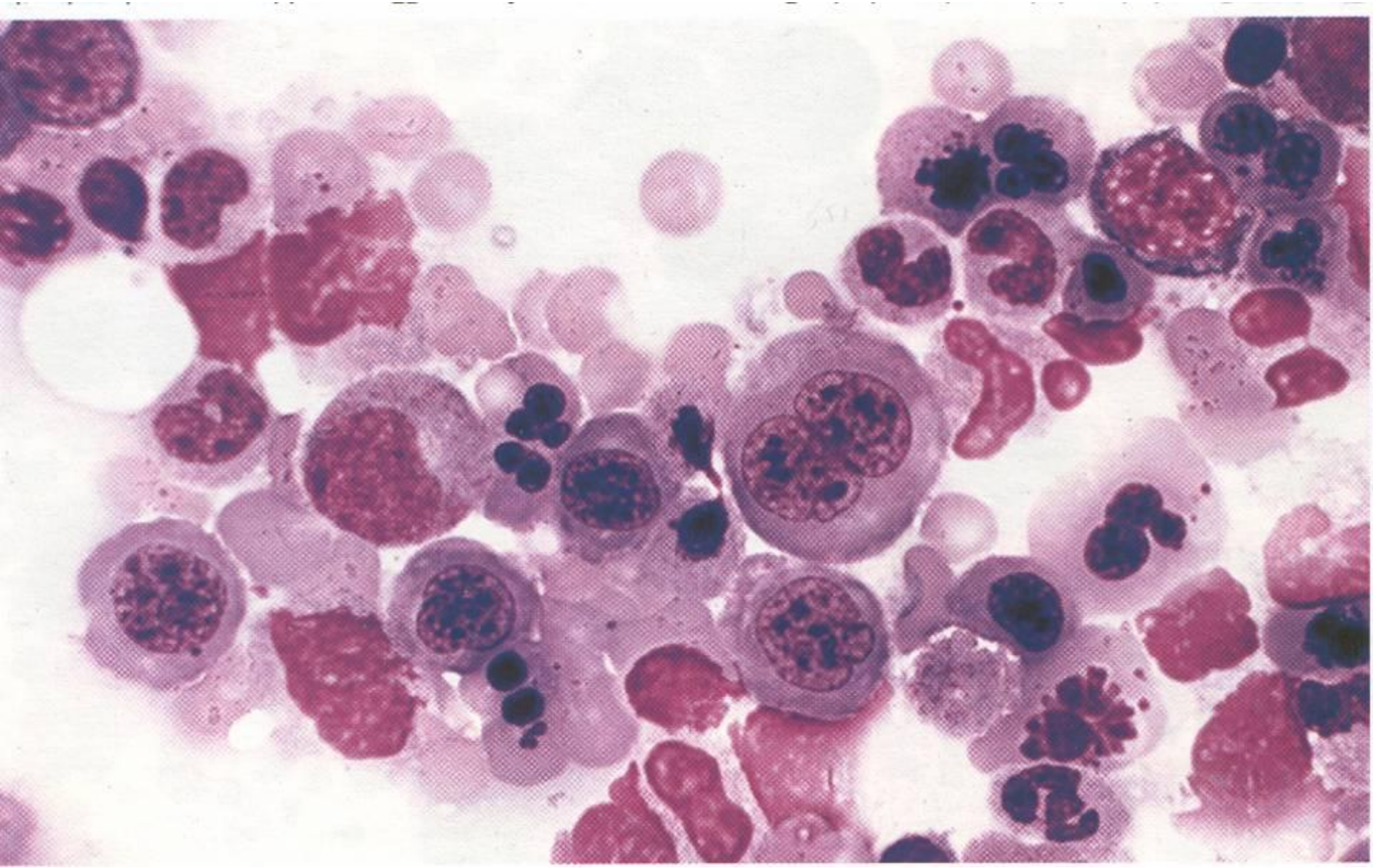
Abnormal localization of immature precursors (ALIP)

Morphology

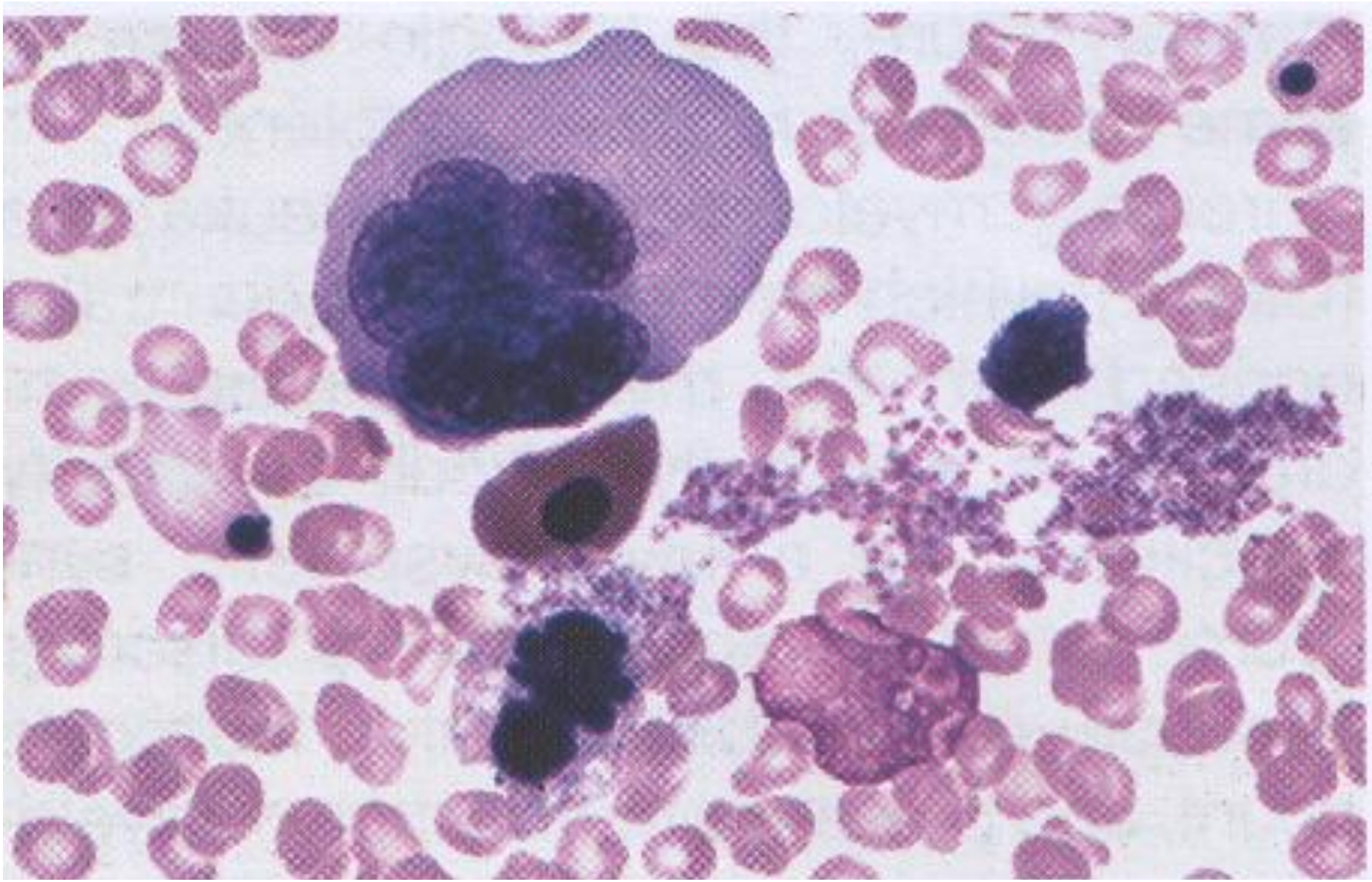
- Exclude non-clonal disorders with dysplastic changes:
  - Congenital dyserythropoietic anemia (CDA)
  - Parvovirus B19
  - G-CSF: hypergranular PMNs, Dohle bodies, +/- increased blasts
  - PNH
  - Chemical & toxic exposure/ medication (esp. chemo)
  - B12 / folate deficiency

Dyserythropoiesis in Arsenic toxication



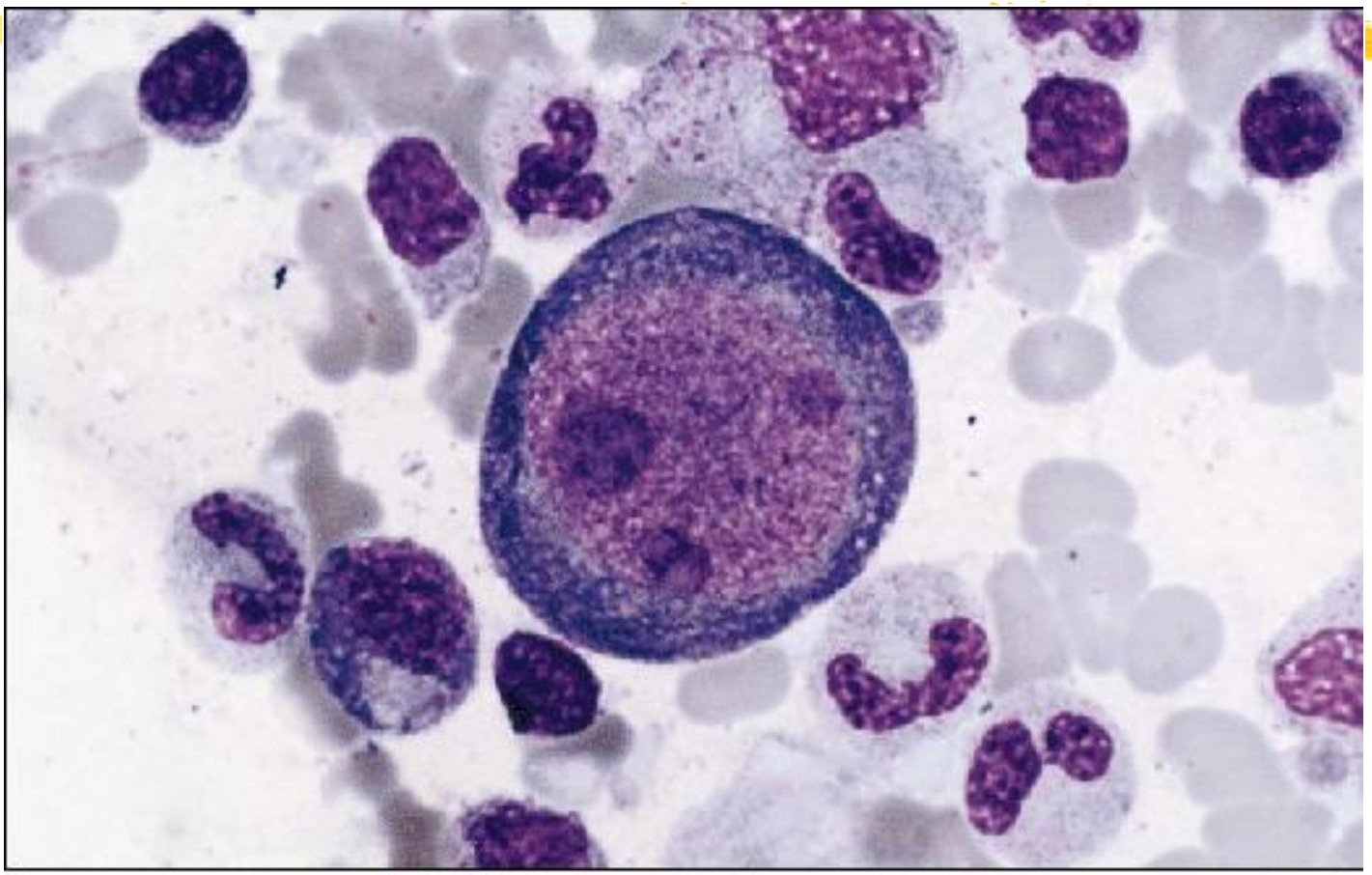


Drug Induced Dyserythropoiesis

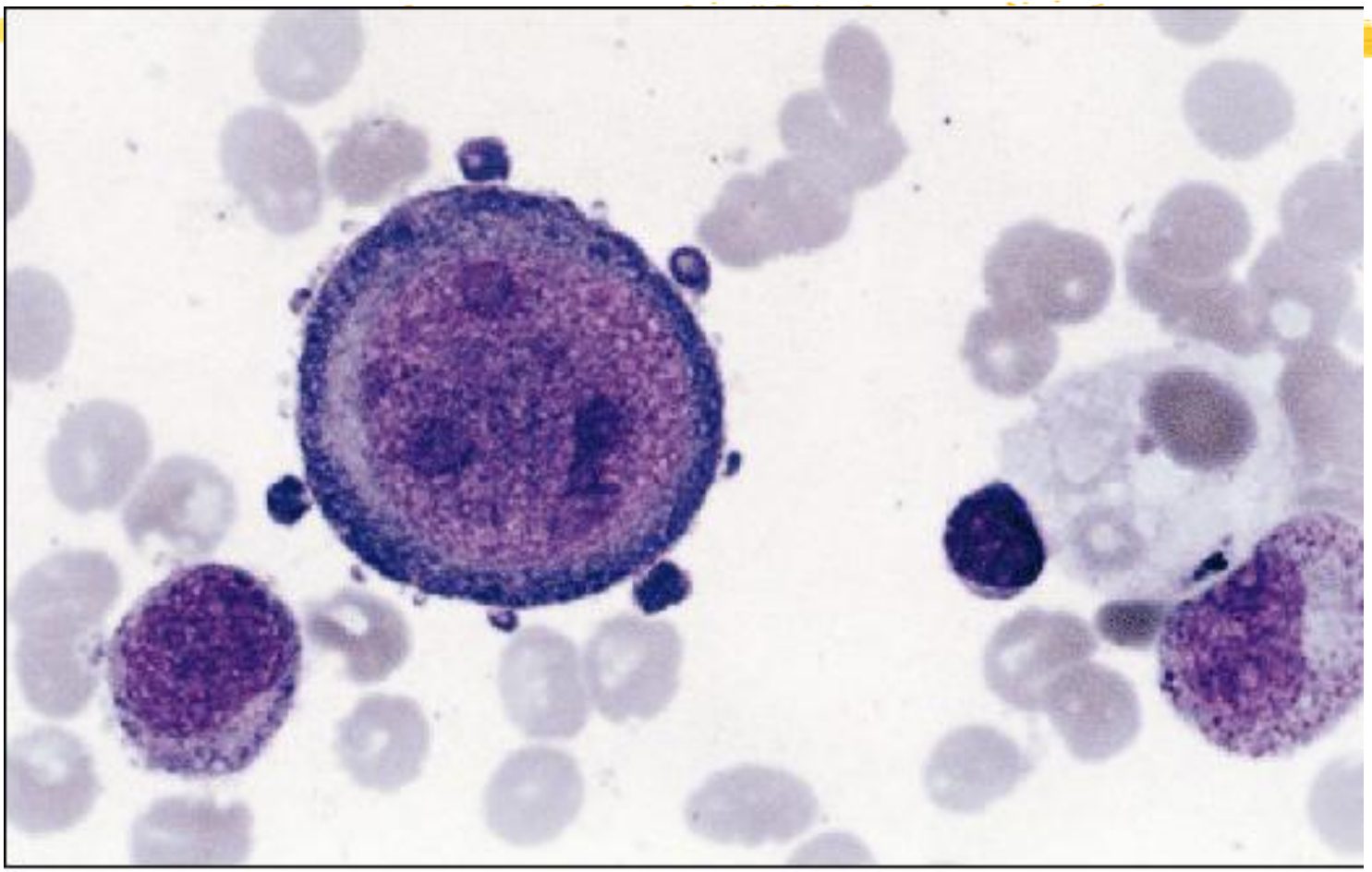


Dyserythropoiesis, congenital dyserythropoietic anemia

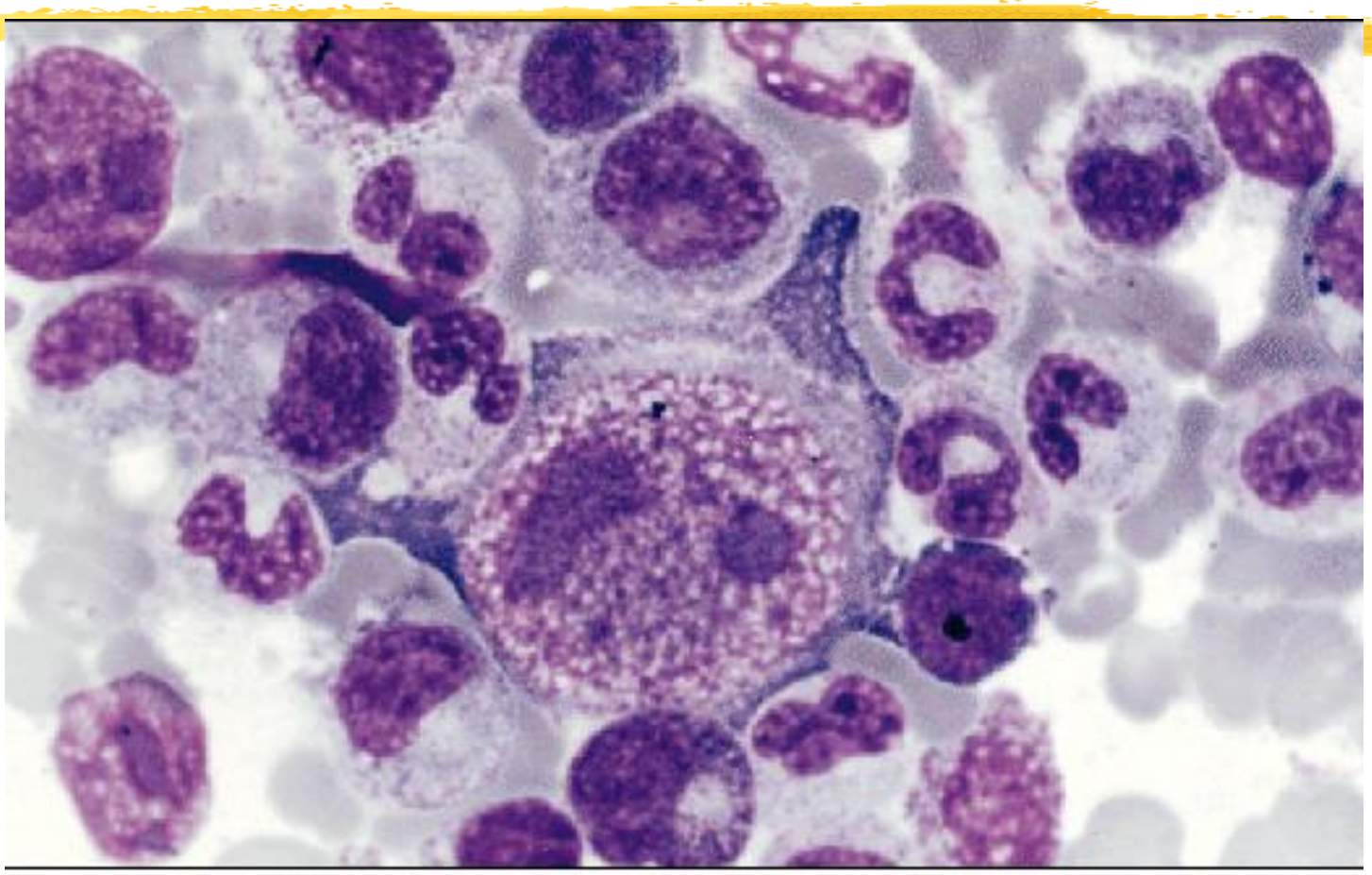
Parvo Virus B19 infection

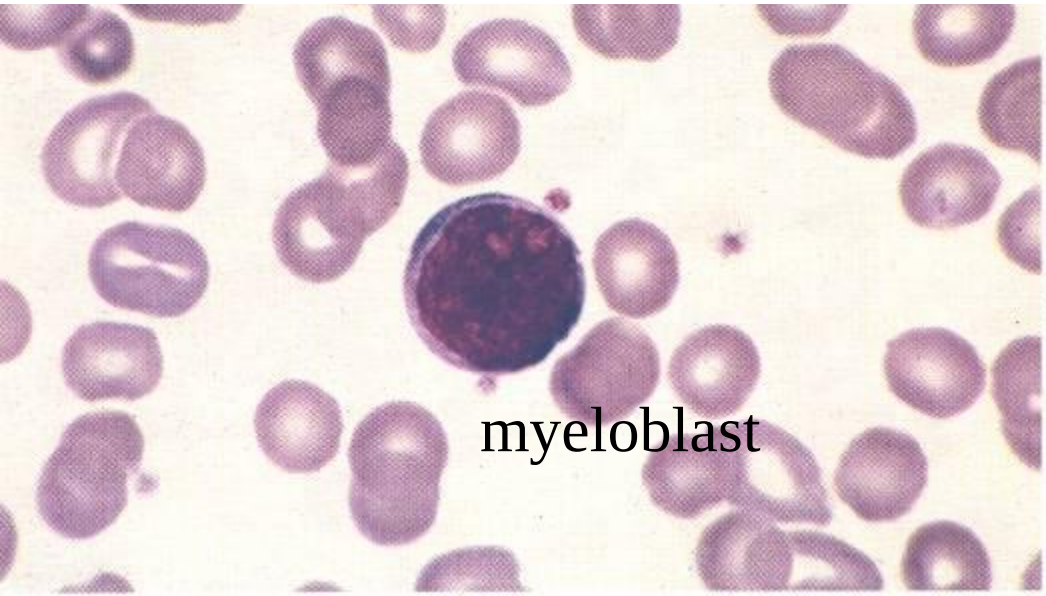


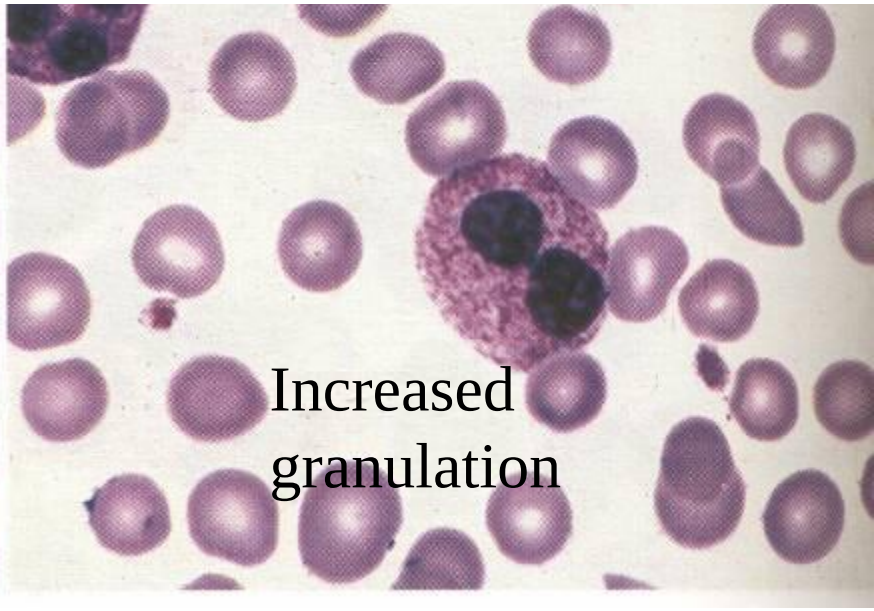
Parvo Virus B19 infection



Parvo Virus B19 infection







G-CSF effect

Morphology:Technical consideration

- Blast count:
  - Blood, 200 cells differential
  - BM: 500 cells differential
- Cytogenetics association:
  - Del(5q): hypolobated megakaryocytes
  - Del(17p): pseudo Pelger-Huet anomaly, or hypolobated neutrophils

International Prognostic Scoring System for MDS
(International MDS Working Group)

- **Blast count**
- **Karyotype**:
  good: normal, -Y,-5q, -20q
  poor:>=3 chromosal abnormalities, chromosome 7
  intermediate: others
- **Cytopenias**: Hb<10 g/dL; N<1,800 /mL; Plt <100k /mL
- **Scores** (high means worse prognosis):
  - Low: 0
  - Int-1: 0.5-1
  - Int-2: 1.5-2
  - High: >=2.5

International Prognostic Scoring System for MDS

SCORE	0	0.5	1	1.5	2
BM blasts (%)	<5	5-10		11-19	20-30
Karyotype	good	intermediate	poor		
Cytopenia	0-1	2-3			

Recurrent Chromosomal Abnormalities in MDS

Unbalanced

- -7 or del(7q)
- -5 or del(5q)
- i(17q) or t(17p)
- -13 or del(13q)
- del(11q)
- del(12p) or t(12p)
- del(9q)
- idec(X)(q13)

Balanced

- t(11;16)
- t(3;21)
- t(1;3)
- t(2;11)
- inv(3)
- t(6;9)

Chromosomal Abnormalities Not Considered as Definitive in MDS

- +8
- del(20q)
- -Y

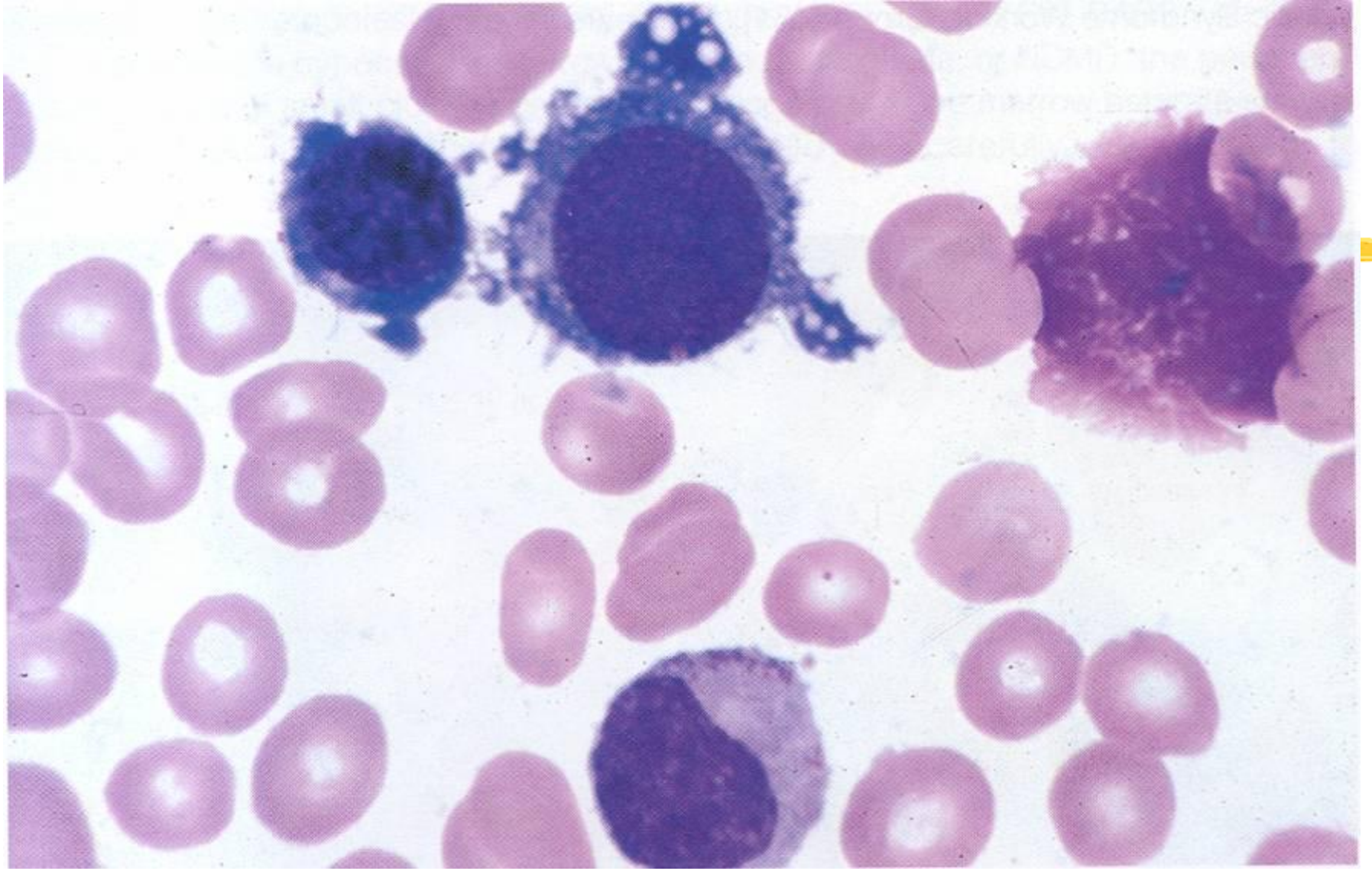
Refractory Anaemia (RA)

Refractory Anaemia (RA)

- Definition: unequivocal dyserythropoiesis
- Exclude: drug, toxin, viral, immunologic, congenital disorders, Vitamin (B12, folate) deficiency
- Blasts:
  - Blood<1%
  - BM<5%

Refractory Anaemia (RA)

- Epidemiology:
- 5-10% of MDS
- Etiology: in most cases unknown
- Sites: blood and BM
- Immunophenotype: not useful
- Genetics: up to 50%(-20q, +8, abnormality 5,7)
- Mean survival: 66 months



RA: dysplasia of erythroid precursors; erythroblast with vacuolated cytoplasm, Bone marrow aspirate

Refractory Neutropenia (RN)

Refractory Neutropenia (RN)

- Definition: >10% dysplastic neutrophils in PB or BM. Other cell lines show minimal dysplasia
- Blasts:
  - Blood<1%
  - BM<5%
- Exclude: drug, toxin, viral, immunologic disorders
- Data on genetics and prognosis are insufficient

Refractory Thrombocytopenia (RT)

Refractory Thrombocytopenia (RT)

- Definition: >10% dysplastic megakaryocytes in BM. Other cell lines show minimal dysplasia
- Blasts:
  - Blood<1%
  - BM<5%
- Exclude: drug, toxin, viral, immunologic disorders
- Data on genetics and prognosis are insufficient

Refractory anaemia with ring-sideroblasts (RARS)

Refractory anaemia with ring-sideroblasts(RARS)

- **Definition:**
- RA plus presence of ring-sideroblasts (RS) in >15% of erythroid precursors
- RS:
  - >=5 siderotic granules;
  - >=1/3 of nuclear circumference
- Blasts in BM <5%
- Rule out: antituberculosis (Isoniazid), alcoholism, congenital disorder (sideroblastic anemia), chemical exposure (lead, benzene)

Refractory anemia with ring-sideroblasts (RARS)

- **Epidemiology**: 10% of MDS
- **Sites**: blood, BM
- **Clinical features:** moderate anemia, progressive iron overload
- Etiology: in most cases unknown
- **Immunophenotype:** not relevant
- Genetics: 5-20% abnormal
- **Prognosis:** median survival: 69-108 months; 1-2% transforms to leukemia

RARS

- PB Morphology
  - Dimorphic:
    - Normochromic RBC (major population)
    - Hypochromic RBC (minor population)
  - Normocytic or macrocytic anemia
  - No blasts

RARS

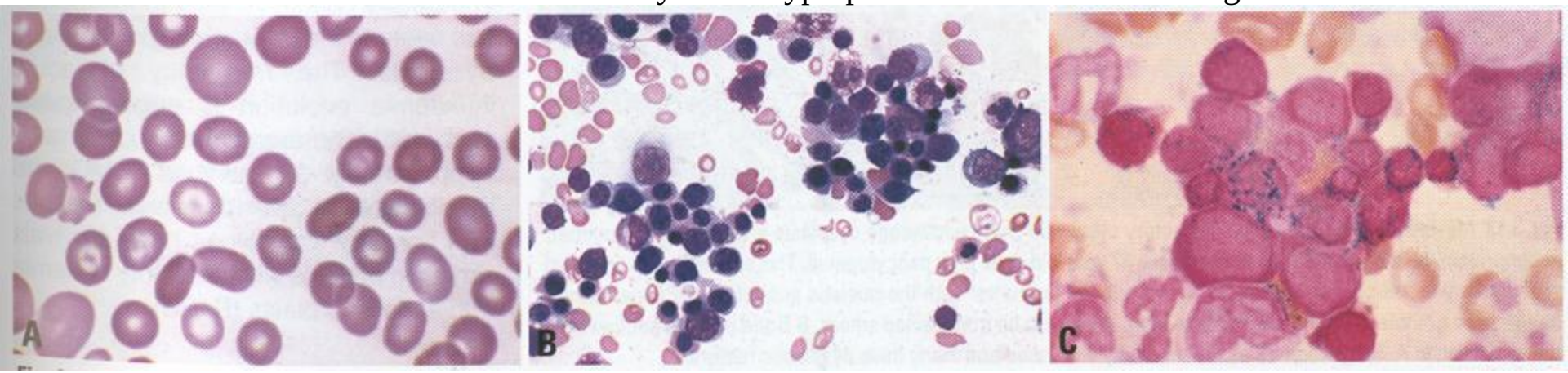
- BM morphology
  - Erythroid hyperplasia
  - Presence of ring-sideroblasts in >15% of erythroid precursors
  - Dysplasia, restricted to erythroid lineage
    - Ring-sideroblasts
    - Nuclear lobation
    - Megaloblastoid features
  - <5% blasts

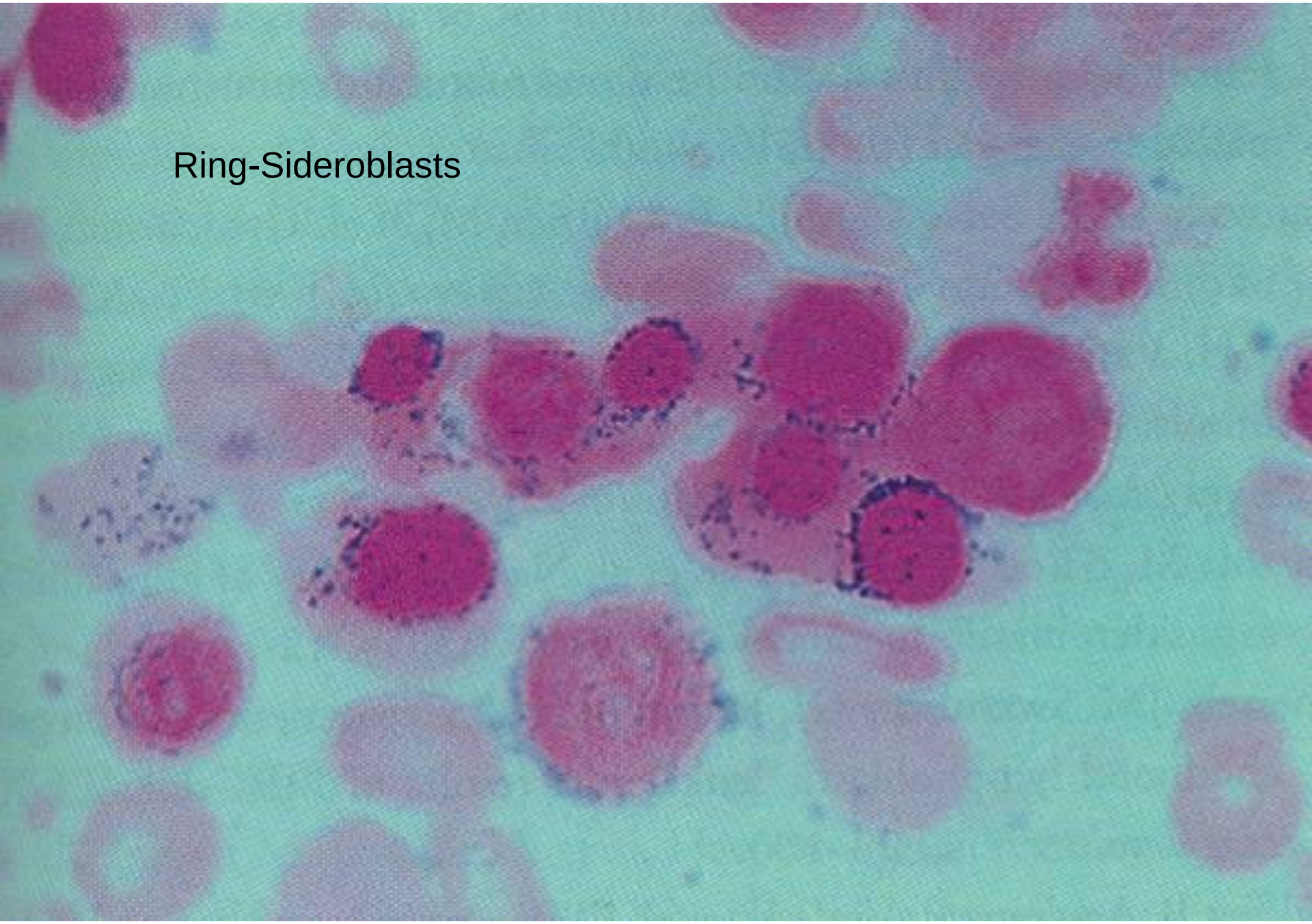
Refractory anaemia with ringed sideroblasts (RARS)

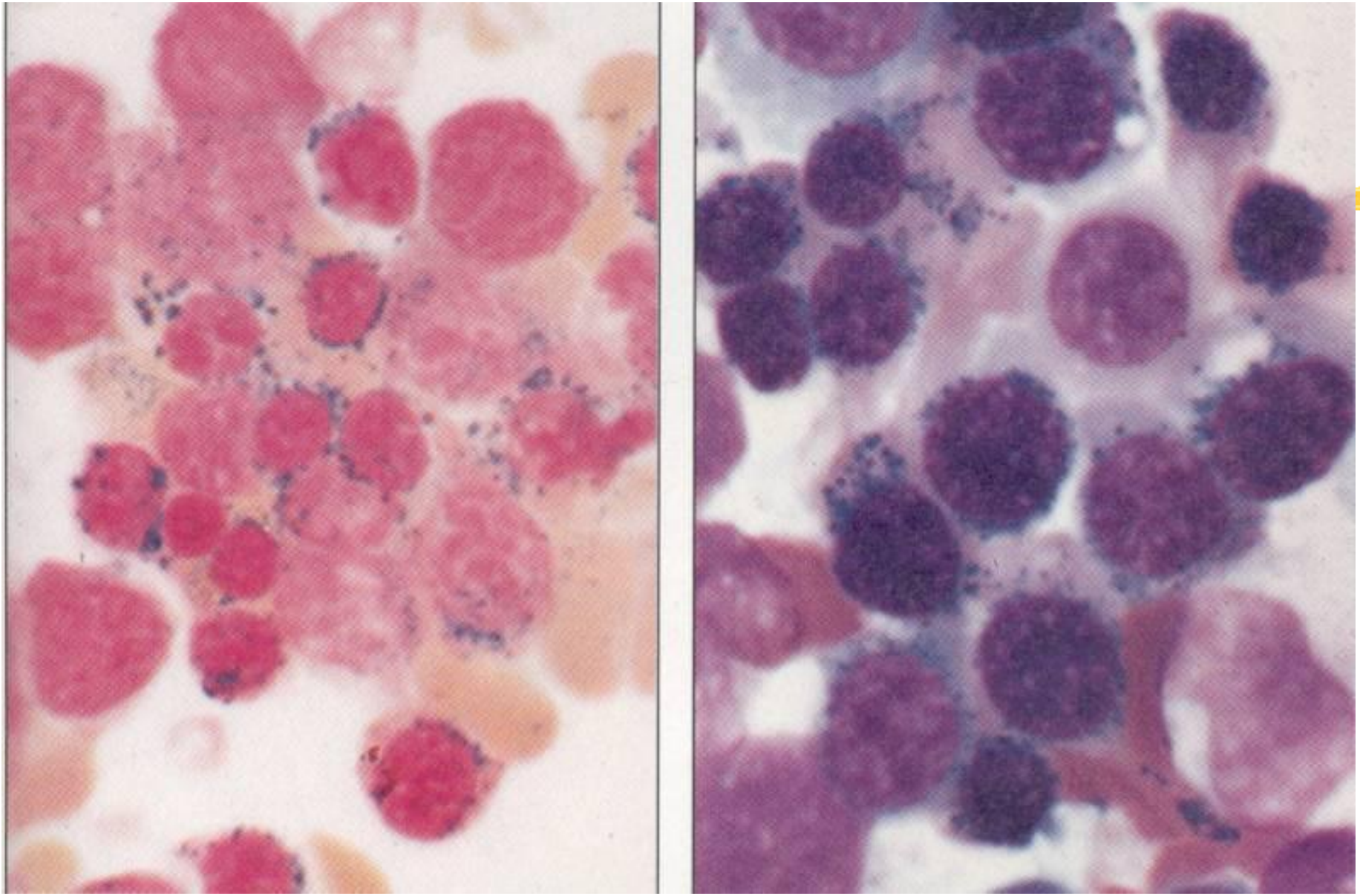
PB: Dimorphic RBCs

BM: Erythroid hyperplasia

BM: Ring-sideroblasts




Ring-Sideroblasts



RARS: ring-sideroblasts,
Bone marrow aspirate

Wright’s counterstain

Refractory Cytopenia with Multilineage Dysplasia (RCMD)

RCMD

- Morphology
  - Dysplastic changes in ≥10% of the cells in ≥2 myeloid cell lines
  - Neutrophils may show
    - Hypogranulation and/or hyposegmentation
  - Erythroids may show
    - Cytoplasmic vacuoles
    - Marked nuclear irregularity including
      - Multilobation
      - Multinucleation
      - Megaloblastoid nuclei

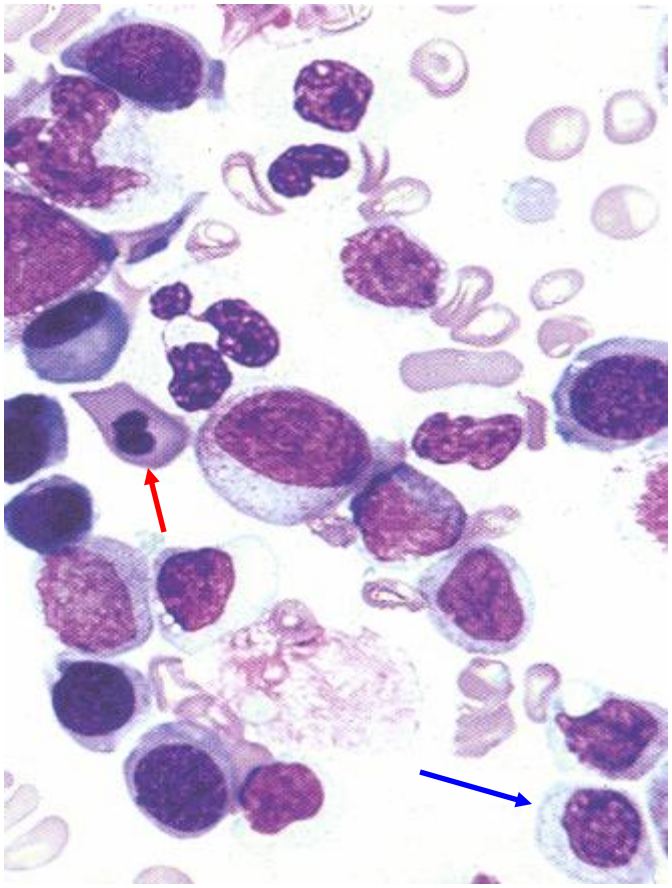
RCMD

- Morphology (cont'd)
  - Megakaryocytes may show
    - Hypolobation
    - Small size
  - Blasts <5%
  - If RS>=15% -> RCMD with RS

RCMD

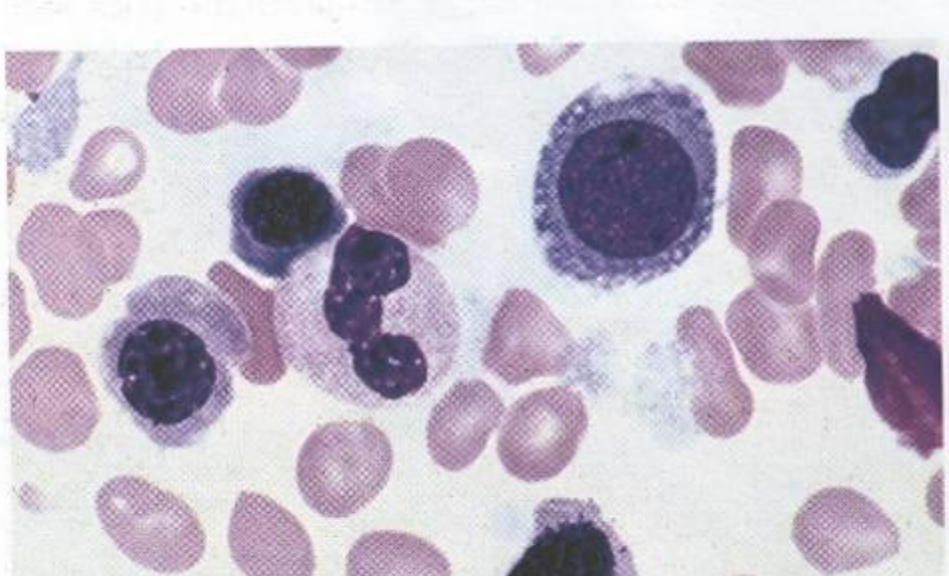
- Genetics: up to 50% (-20q, +8, abnormality 5, 7, complex karyotypes)
- Median survival: 30 months, 10% transformed to AML in 2 yrs

RCMD: **Bone marrow aspirate**

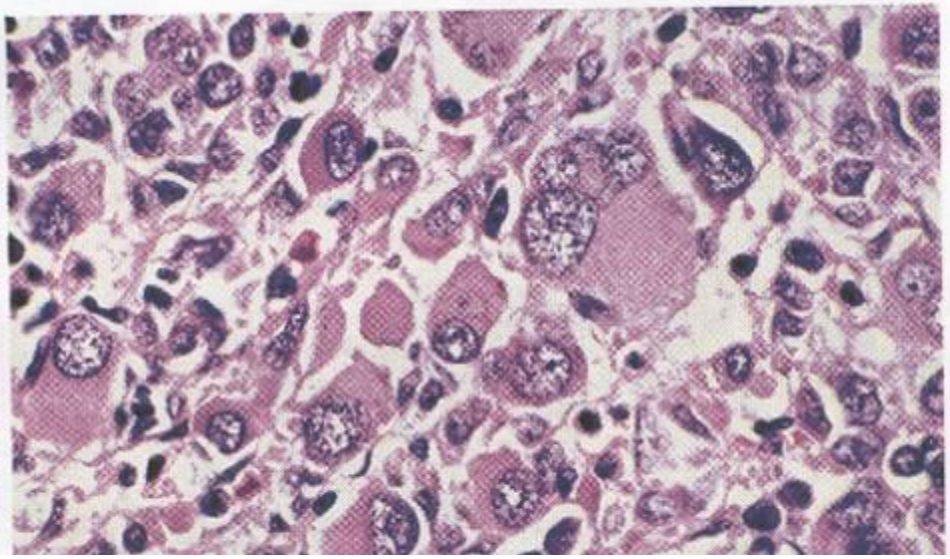


Multilineage dysplasia:
Erythroid dysplasia
Neutrophils with hypolobulated nuclei

RCMD



A. Bone marrow aspirate with dysplastic erythroids



B. Bone marrow biopsy with increased dysplastic megakaryocytes

Refractory Anemia with Excess Blasts (RAEB)

RAEB

- PB Morphology
  - Unilineage- or multilineage abnormalities
    - Anisopoikilocytosis with macrocytes
    - Hypogranulation and/or nuclear hyposegmentation
    - Atypical platelets (hypogranular)
    - 0-19% blasts

RAEB

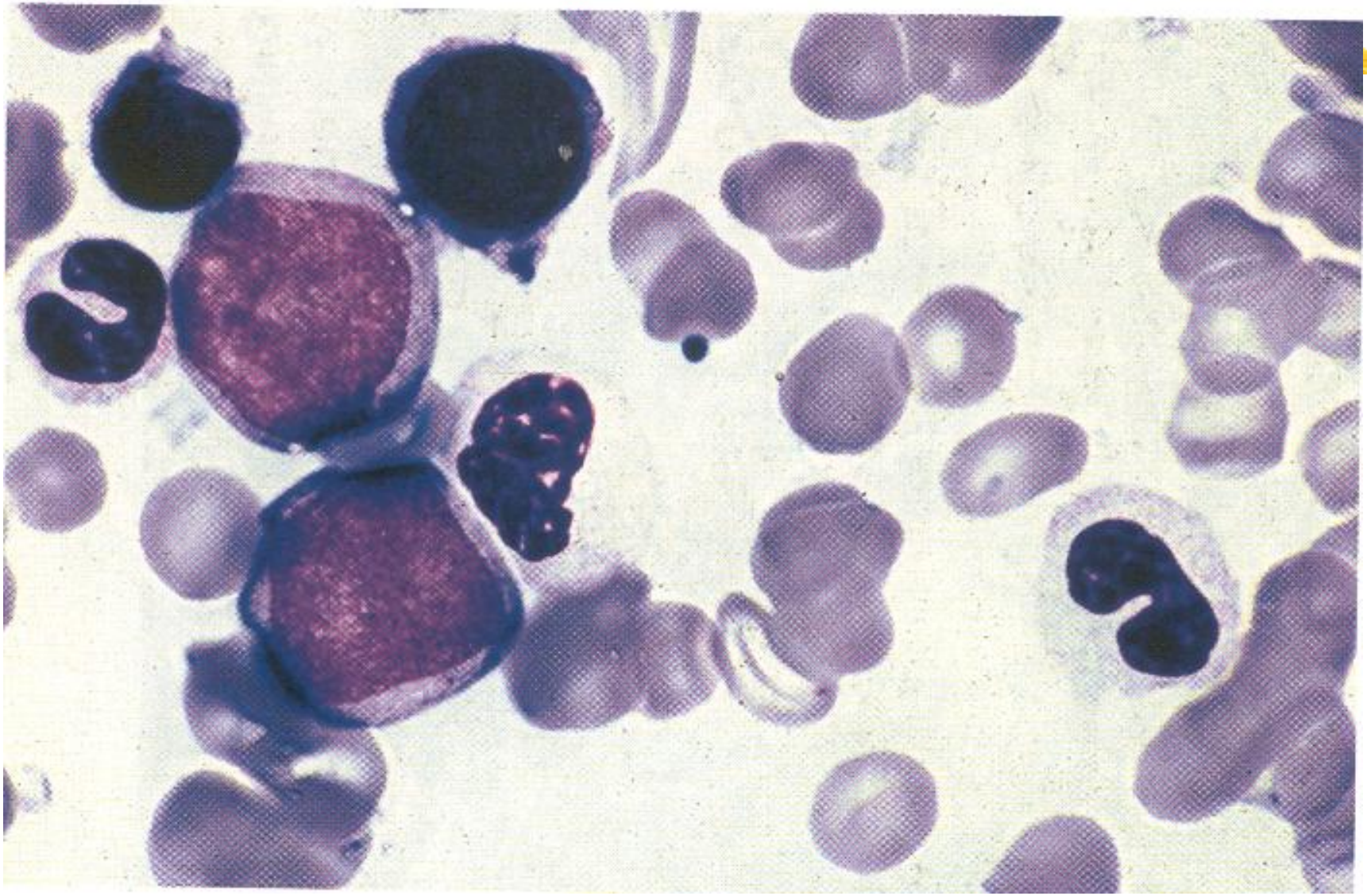
- BM Morphology
  - Usually hypercellular (hypocellular in 10-15%)
  - Dysplasia in all 3 cell lines
  - 5-19% blasts (myeloid phenotype: CD-13/33/117)
  - May have abnormal localization of immature precursors (ALIP)

RAEB

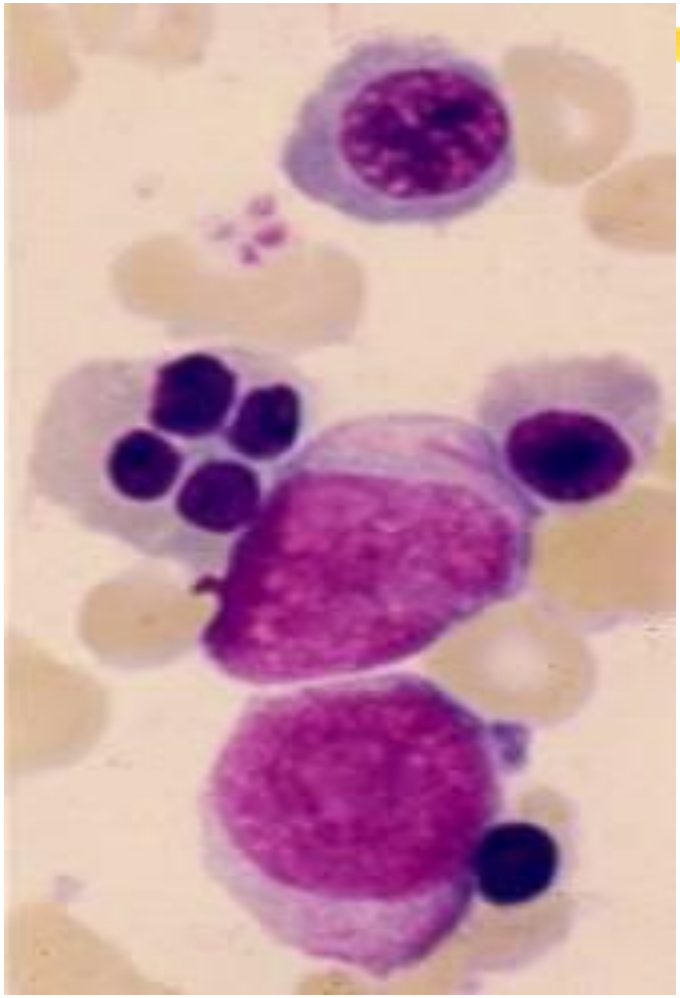
- Subtypes:
  - RAEB-1, Blasts: <5% (blood) or 5-9% (BM)
  - RAEB-2, Blasts: 5-19%(blood) or 10-19% (BM)

    ***RAEB-1 and myeloblasts with auer rods should be upgraded to RAEB-2

RAEB-1, bone marrow

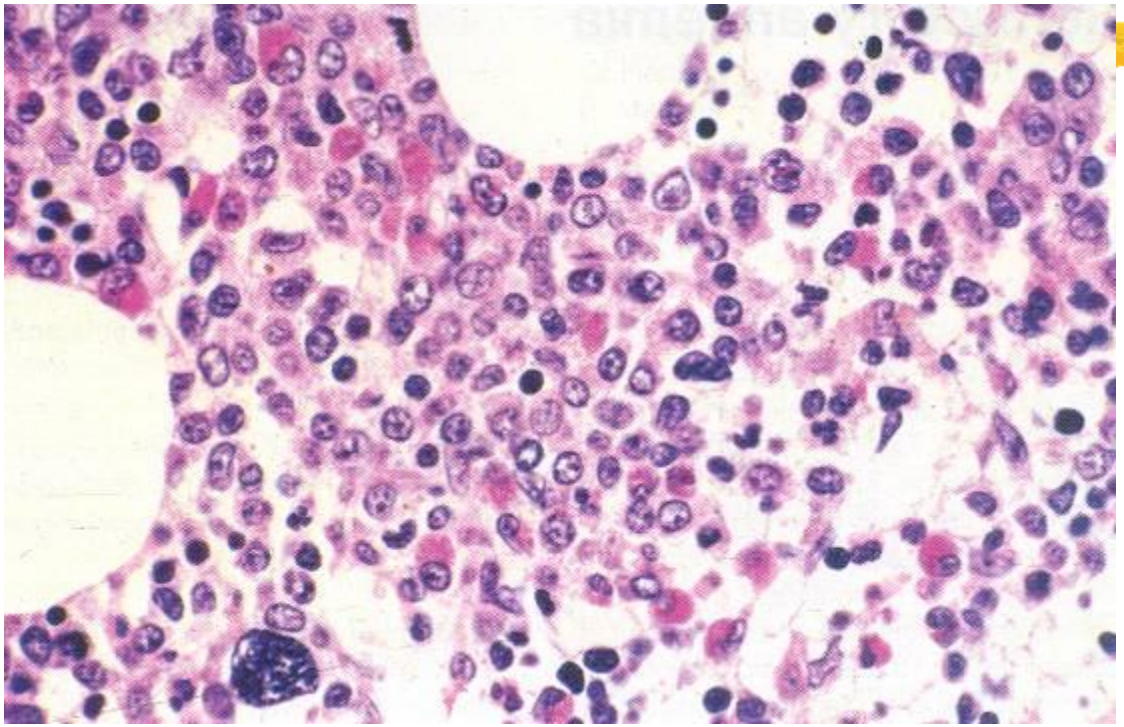


RAEB-2



Two myeloblasts,
one with an Auer rod,
and a quadrinucleate normoblast

ALIP



Abnormal localization of immature precursors (ALIP):
Immature myeloid cell clusters (5-8 cells) present in central portion of marrow away from usual locations (paratrabecular or perivascular) three or more clusters/ section → positive for ALIP

ALIP

- Frequently present in RAEB
- Associated with rapid evolution to AML
- If found in other subtypes, blast count in aspirate may have been inaccurate
  - Re-evaluate
    - Peripheral blood smear
    - Bone marrow aspirate smear

RAEB

- Genetics: 30-50%, including +8, -5, del(5q), -7, del(7q), del(20q), or complex karyotypes
- Median survival:
  - RAEB-1: 16 months
  - RAEB-2: 9 months

Myelodysplastic syndrome with isolated del (5q)

Myelodysplastic syndrome with isolated del (5q)

- A myelodysplastic syndrome a/w an isolated del(5q)
- <5% blasts in PB and BM

Myelodysplastic syndrome with isolated del (5q)

- Epidemiology
  - Middle age to older women (predominantly but not exclusively)

Myelodysplastic syndrome with isolated del (5q)

- Clinical features
  - Refractory anemia, severe (accounts for most common symptoms)
  - Significant increase in platelet count, occasionally normal

Myelodysplastic syndrome with isolated del (5q)

- PB Morphology
  - Marked macrocytic anemia
  - Slight leukopenia
  - Platelet count increase (sometimes normal)
  - <5% blasts

Myelodysplastic syndrome with isolated del (5q)

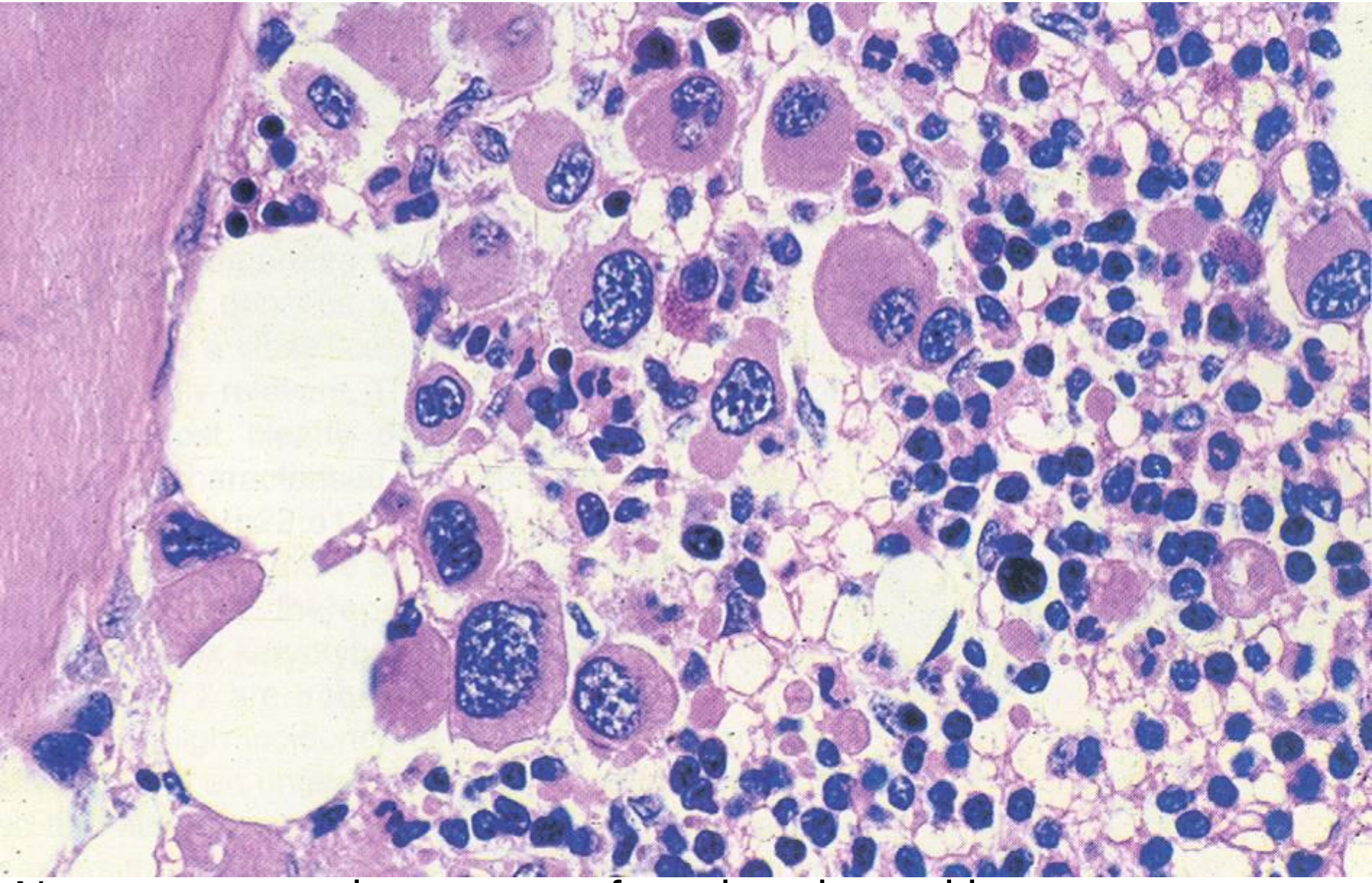
- BM Morphology
  - Normocellular or hypercellular
  - Megakaryocyte number increase (or normal), many hypolobated
  - Variable degree of erythroid dysplasia
  - <5% blasts
  - Scattered aggregates of small lymphocytes

Myelodysplastic syndrome with isolated del (5q)

- Genetics
  - Del(5q), between bands q31 and q33
  - Break points and size of deletion are variable
  - No other cytogenetic abnormalities, by definition

Myelodysplastic syndrome with isolated del (5q)

- Prognosis and predictive factors
  - Long survival: median 145 months
  - Karyotypic evolution is uncommon (if additional cytogenetic abnormalities are found subsequently -> evolution to AML or higher grade MDS)
  - Significance of isolated del(5q) and >5% blasts is not clear



Numerous megakaryocytes of varying sizes with hypolobulated nuclei, bone marrow biopsy

Myelodysplastic syndrome, unclassified (MDS-U)

MDS-U

- Definition
  - Myelodysplastic syndrome which lacks findings appropriate for classification as RA, RN, RT, RARS, RCMD, RAEB
  - For example:
    -Pancytopenia with only erythroid dysplasia (RCUD)
    -Cases with minimal dysplasia a/w recurrent cytogenetic abnormalities
    -Cases with findings of RCUD plus 1% blasts in PB