Myelodysplastic Syndrome

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Myelodysplastic Syndrome (MDS)

- Criteria for diagnosis of MDS
- Pathophysiology of MDS.
- Clinical manifestation of MDS.
- Chromosomal abnormalities in MDS.
- Classification of MDS
- Risk factors and prognosis score of MDS.
- Treatment of MDS.

Myelodysplastic syndrome

- A heterogeneous group of hematopoietic disorders characterized by peripheral blood cytopenias and hypercellular marrow
- Clonal malignant disorder of the hematopoietic cells
- Transformation to AML is frequent

Characteristics

- Varying degree of tri-lineage cytopenia (red blood cells, white blood cells and platelets).
- Dysplasia
- Normocellular or hypercellular B.M.
- May progress to acute leukaemia

Signs and Symptoms

- Excessive tiredness, shortness of breath, and pale skin can be caused by anemia (shortage of red blood cells).

- Serious infections with high fevers can be caused by *leukopenia* (not having enough normal white blood cells) and, in particular, by having *neutropenia* or *granulocytopenia* (too few mature granulocytes).

- Excessive bruising and bleeding, for example, frequent or severe nosebleeds and/or bleeding from the gums, can be due to *thrombocytopenia* (not having enough of the blood platelets needed for plugging holes in damaged blood vessels).

INCIDENCE

1- Disease of elderly.

2- Median age is 65 years.

3- <10% are younger than 50 years.

4- Incidence rates 1/100,000 pop./ years.

5- Incidence rise to 1/1000 / years in ≥ 65 years old.

6- Male slightly higher than female

MDS Etiology

- **Two etiologic categories of MDS:**

1.) **De Novo**:

Associated with:

-benzene exposure (gasoline)

-cigarette smoking

-viruses -Fanconi's anemia

2.) **Therapy related**:

Associated with:

-alkylating agent chemotherapy

-radiation

ETIOLOGICAL AGENTS

- Tobacco smoke.
- Ionizing radiation.
- Organic chemicals (such as benzene, toluene, xylene, and chloramphenicol).
- Heavy metals.
- Herbicides.
- Pesticides.
- Fertilizers.
- Stone and cereal dusts.
- Exhaust gases.
- Nitro-organic explosives.
- Petroleum and diesel derivatives.
- **Alkylating agents.**
- **Marrow-damaging agents used in cancer chemotherapy**.

Pathophysiology

- The initial hematopoietic stem cell injury can be from cytotoxic chemotherapy, radiation, virus, chemical exposure, or genetic predisposition.
- A clonal mutation predominates over bone marrow, suppressing healthy stem cells.

MDS Development

Theories of Pathophysiology involved in MDS Development	Potential Targets/Components Involved	Overall Result of Abnormality
Environmental/Aging		
Aging	Increased BM apoptosis	Decreased hematopoietic stem cell pool
Environmental Exposures	Smoking Radiation Benzene Viral Infections Chemotherapy	Direct Toxicity to hematopoietic stem cells.
Telomere Abnormalities	Potential decreased telomerase and subsequent telomere shortening	•Impaired ability to renew stem cell pool. •Genetic Instability

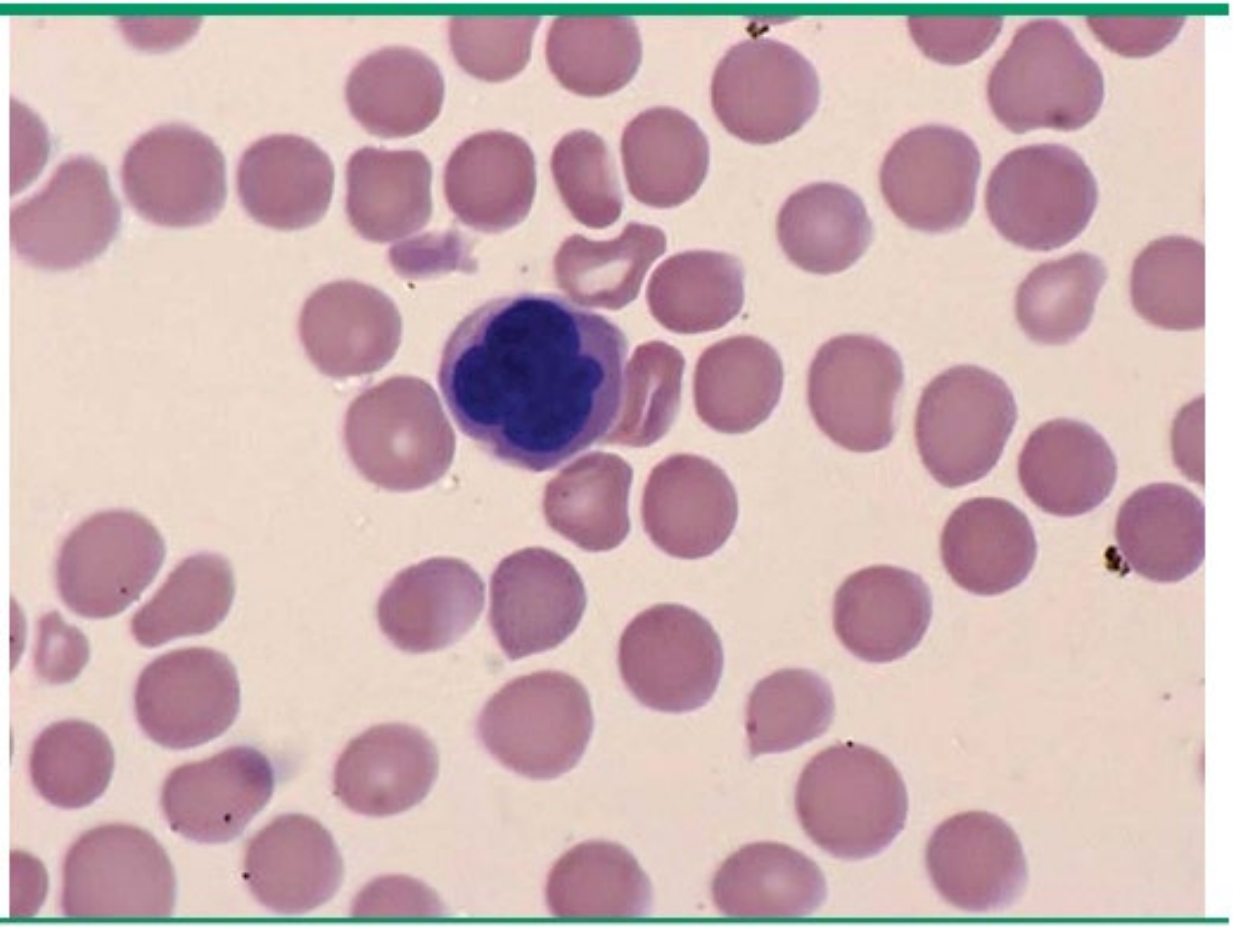
Chromosomal Abnormalities in MDS

Genetic Alterations		
Cytogenetic Abnormalities	**Common Abnormalities:** • 5q- , 20q- • Y- , Trisomy 8 • 7q-/Monosomy7, 17p Syndrome • 11q23, 3q • p53 mutations, Ras mutations • Complex Cytogenetics	• Abnormalities: typically unbalanced genetic loss • Numerous theories of tumor suppressor Loss • Multi-Hit progression from low risk MDS to AML •Genetic Instability
Epigenetic Modulation	**•Hypermethylation** **•Acetylation Alterations**	Methylation and acetylation abnormalities lead to silencing of genes important in cell cycle, differentiation, apoptosis, angiogenesis

Bone Marrow: Pathologic Alterations

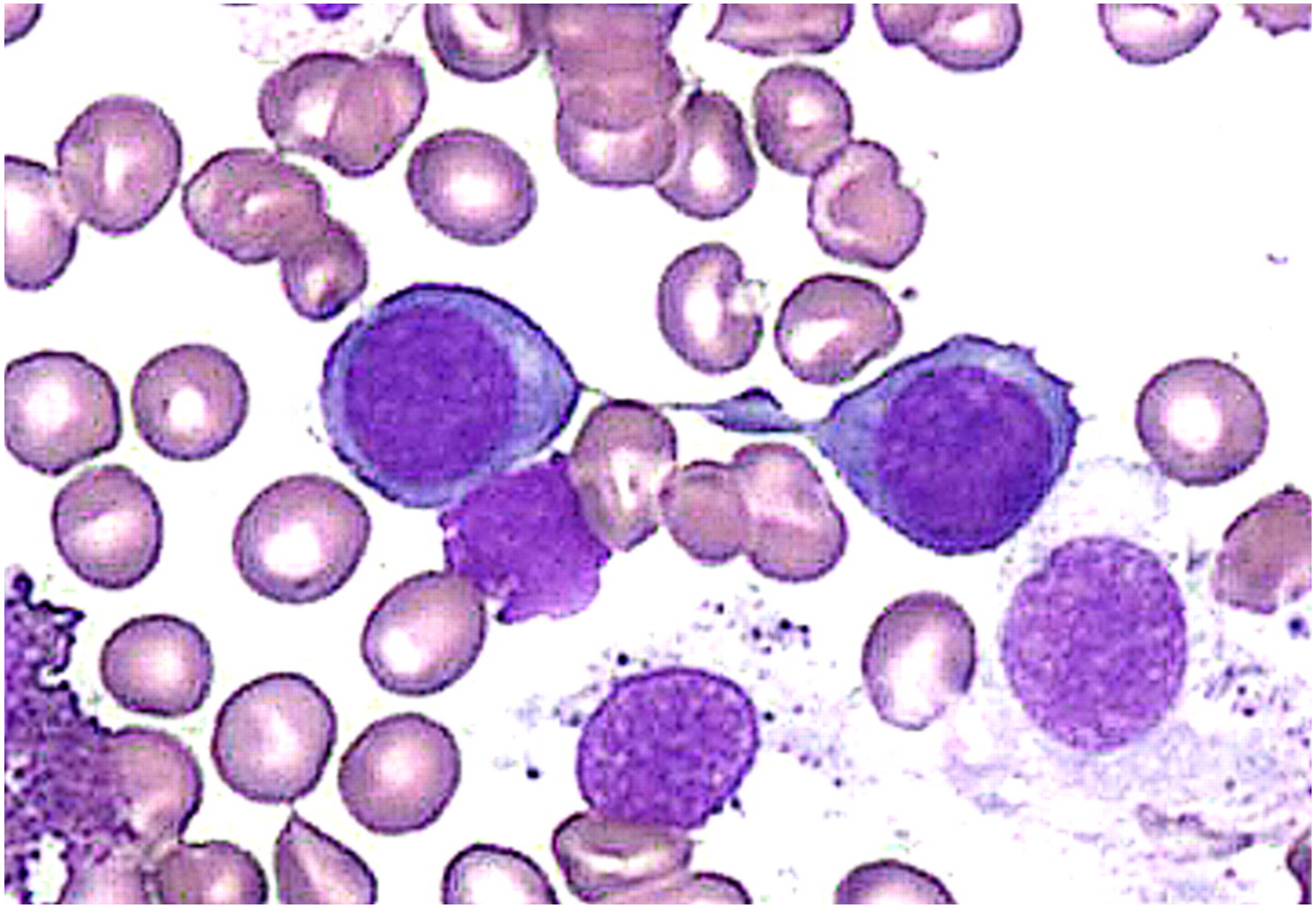
Altered Bone Marrow Microenvironment		
Altered Bone Marrow Microenvironment Cytokines	Upregulation of: TNF-α, IFN-gamma, TGF-Beta, IL-1B, IL-6, Il-11	•Alteration of growth, differentiation, angiogenesis •Immune modulation
Alterations in Apoptosis via Signalling	•Increased TNF-α levels •FAS: Increased Apoptosis •BCL-2 alterations	•Increased apoptosis and proliferation in early stage MDS leading to hypercellular marrow with peripheral cytopenias • Decreased apoptosis and increased proliferation in later stage MDS leading to progression to AML
Increased Angiogenesis	•Increased VEG-F • Possible Increase: gFGF and EGF Angiogenin	Increased Microvessel Density (MVD): role in pathogenesis not clearly elucidated but associated with progression to AML

Dysplastic red blood cell in myelodysplastic syndrome

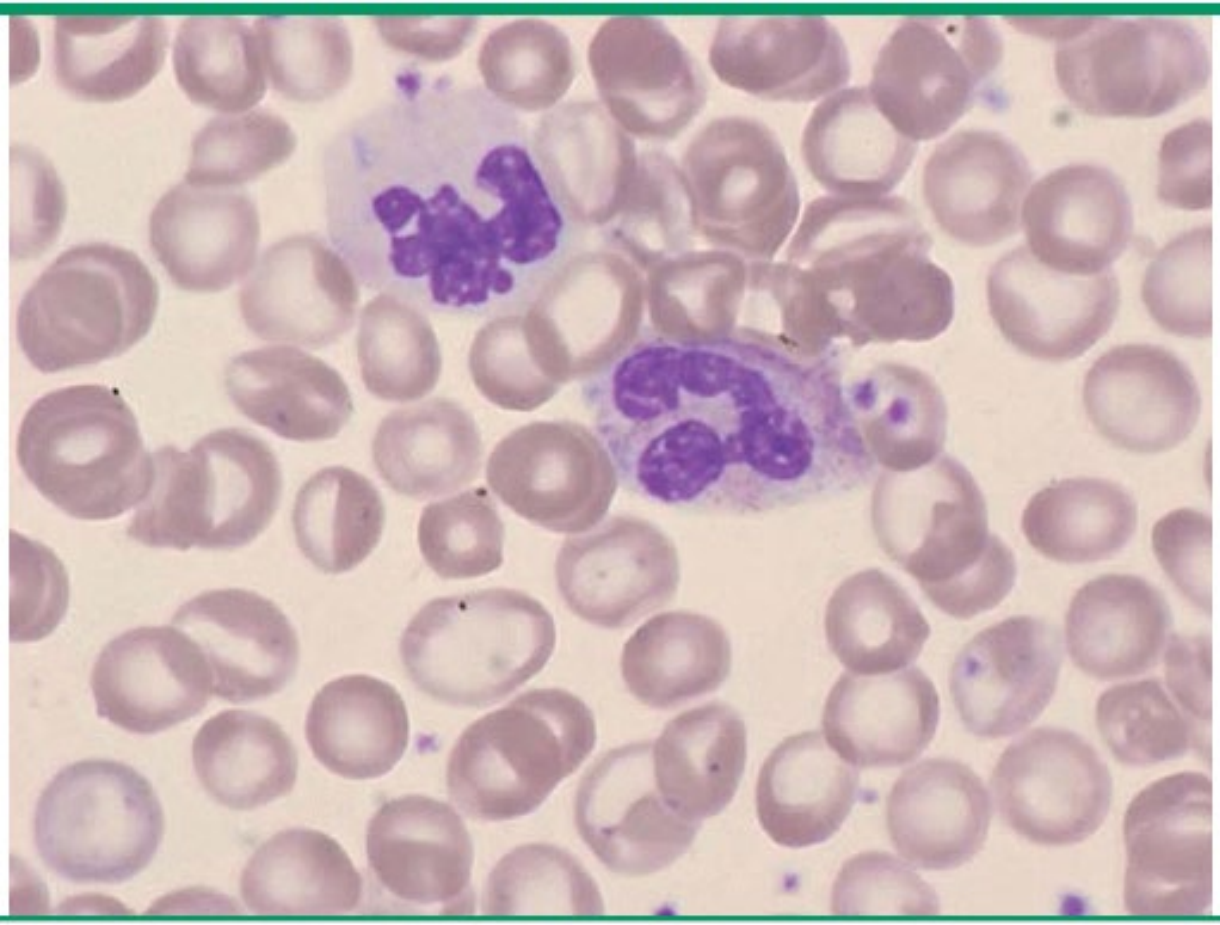


Dysplastic nucleated red blood cell, peripheral blood. The nucleus shows an abnormal shape and size.

MDS with Dyserythropoiesis

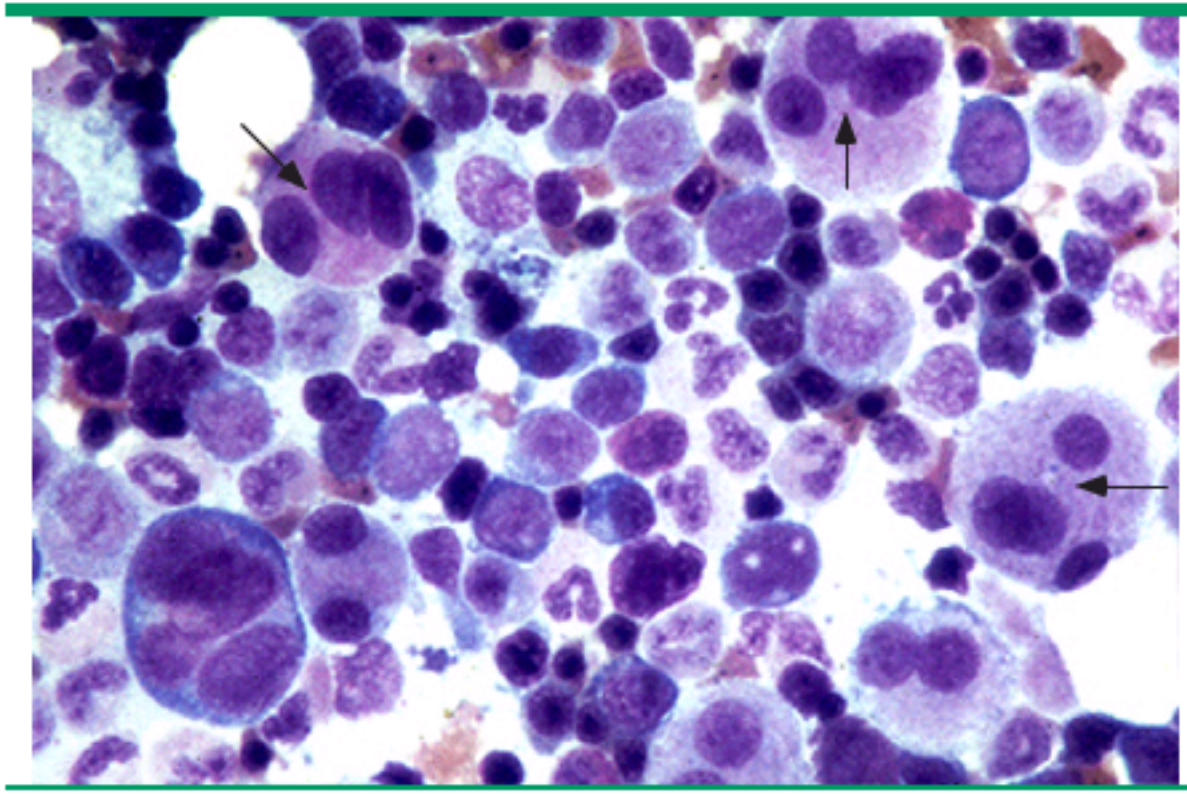


Dysplastic neutrophils in myelodysplastic syndrome



Dysplastic neutrophils, peripheral blood. The cells are nearly agranular. The nuclear segmentation is also abnormal.

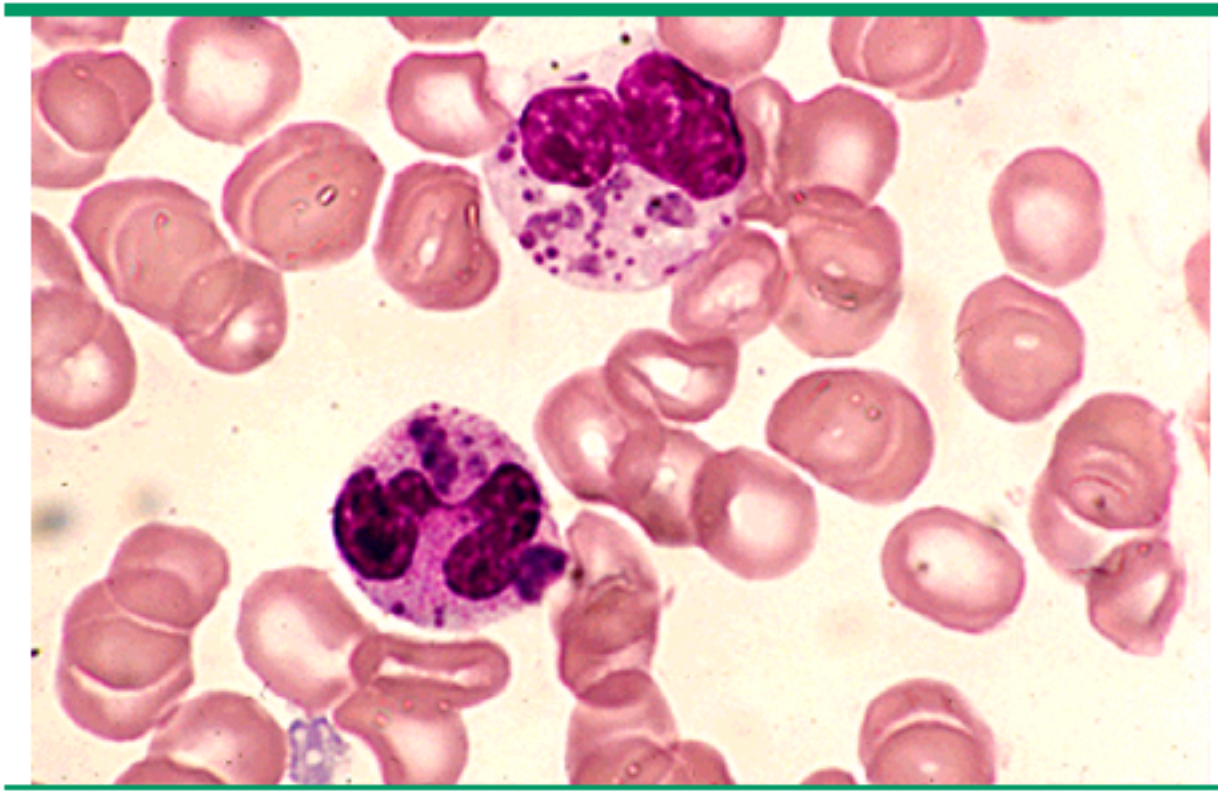
Myelodysplastic syndrome with abnormal megakaryocytic maturation



Bone marrow aspirate from a patient with myelodysplastic syndrome. The megakaryocytes are abnormal, with multiple small lobes seemingly disconnected from each other ("Pawn ball" changes, arrows). (Wright-Giemsa).

Courtesy of David S Rosenthal, MD.

Giant neutrophil granules in Chediak-Higashi syndrome



Peripheral blood smear from a patient with Chediak-Higashi syndrome shows giant granules in the cytoplasm of both a neutrophil and a band form. These granules are formed by the inappropriate fusion of lysosomes and endosomes.
Courtesy of Robert L Baehner, MD.

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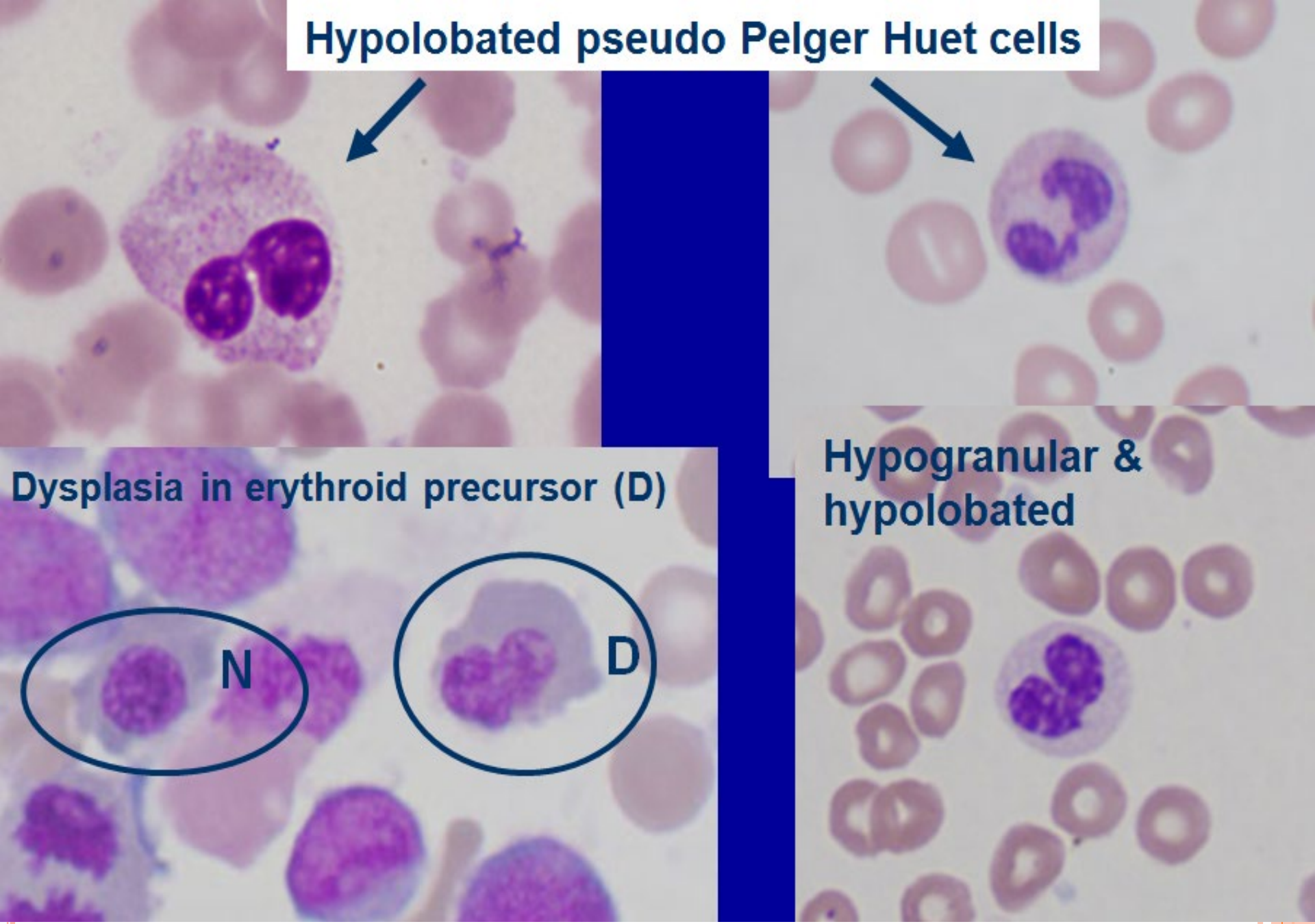
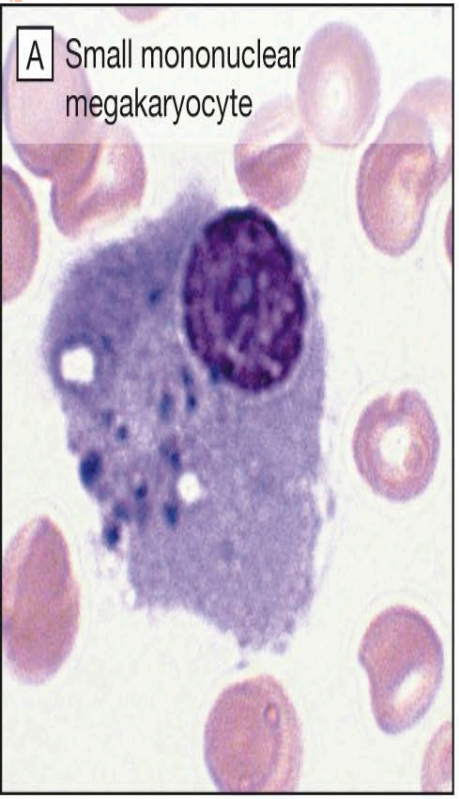
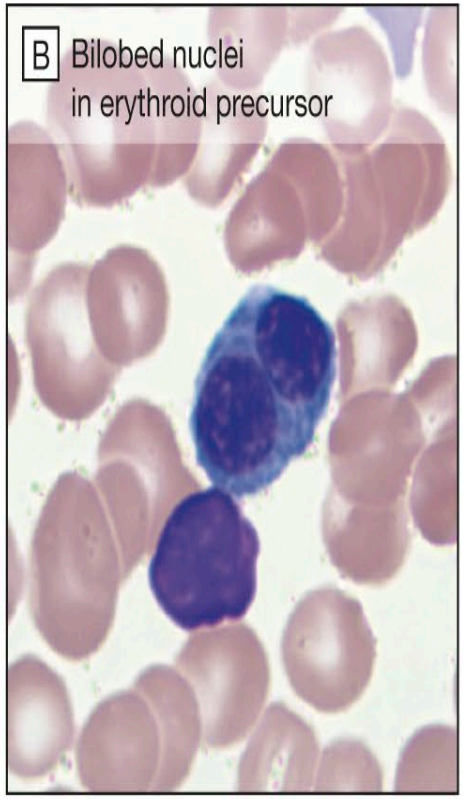
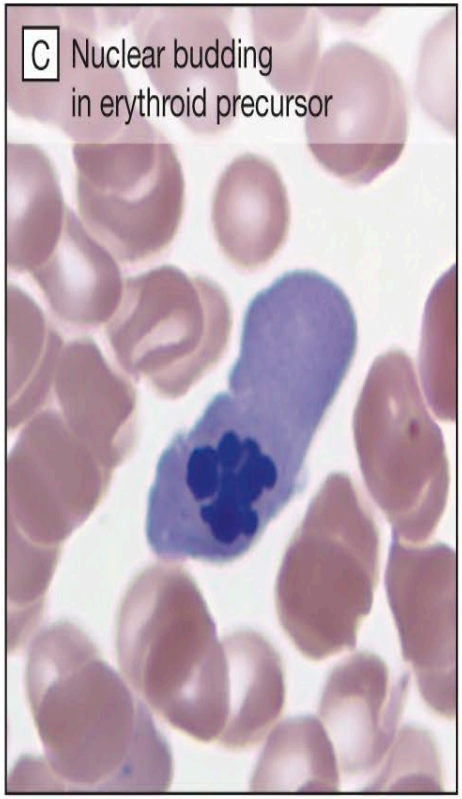
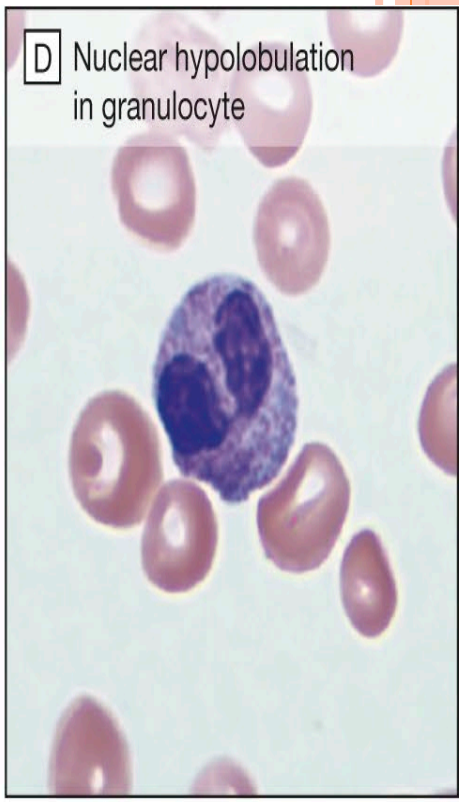

Hypolobated pseudo Pelger Huet cells
Dysplasia in erythroid precursor (D)
N
D
Hypogranular &
hypolobated

Myelodysplastic Syndrome: Findings









Basic Diagnostic Evaluation:

- Peripheral blood counts + reticulocyte count , chemistry, coagulation
- Bone marrow biopsy and aspiration
  - Cytogenetics - FISH, molecular genes
- Auxiliary tests
  - Flow cytometry in indeterminate cases
  - Iron saturation, ferritin
  - B12, folate levels
  - **EPO level (help in diagnosis and therapy)**

Establish diagnosis
Assess
- FAB/WHO classification
- IPSS score (if applicable)
  Inter. Prognostic Index

Peripheral Blood and Bone Marrow Finding

- **Peripheral blood :**

  Red blood cells : ovalmacrocytosis , hypochromia.

  WBCs: promyelocyte and hyposegmentation.

  Platelet: large , dysplastic forms.

- **Bone Marrow**:

  RBCs : erythroid hyperplasia , megaloblastic appearance and dyserythropoiesis with excess sidroblasts.

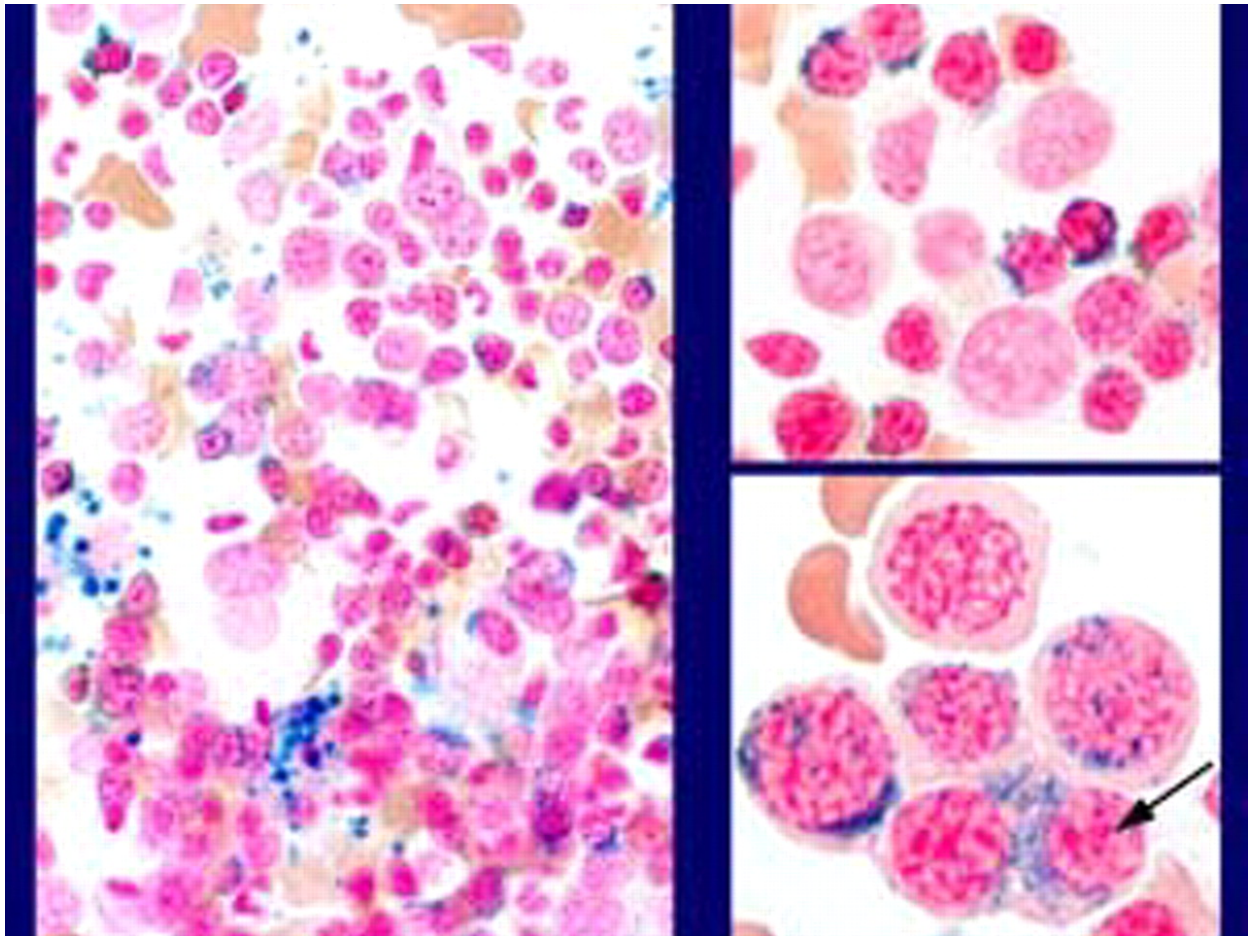
  WBCs: abnormal monocyte maturation and granulocyte maturation bulge.

  Platelet: megakaryocytosis and dysthrombopoiesis.

FAB Classification in MDS

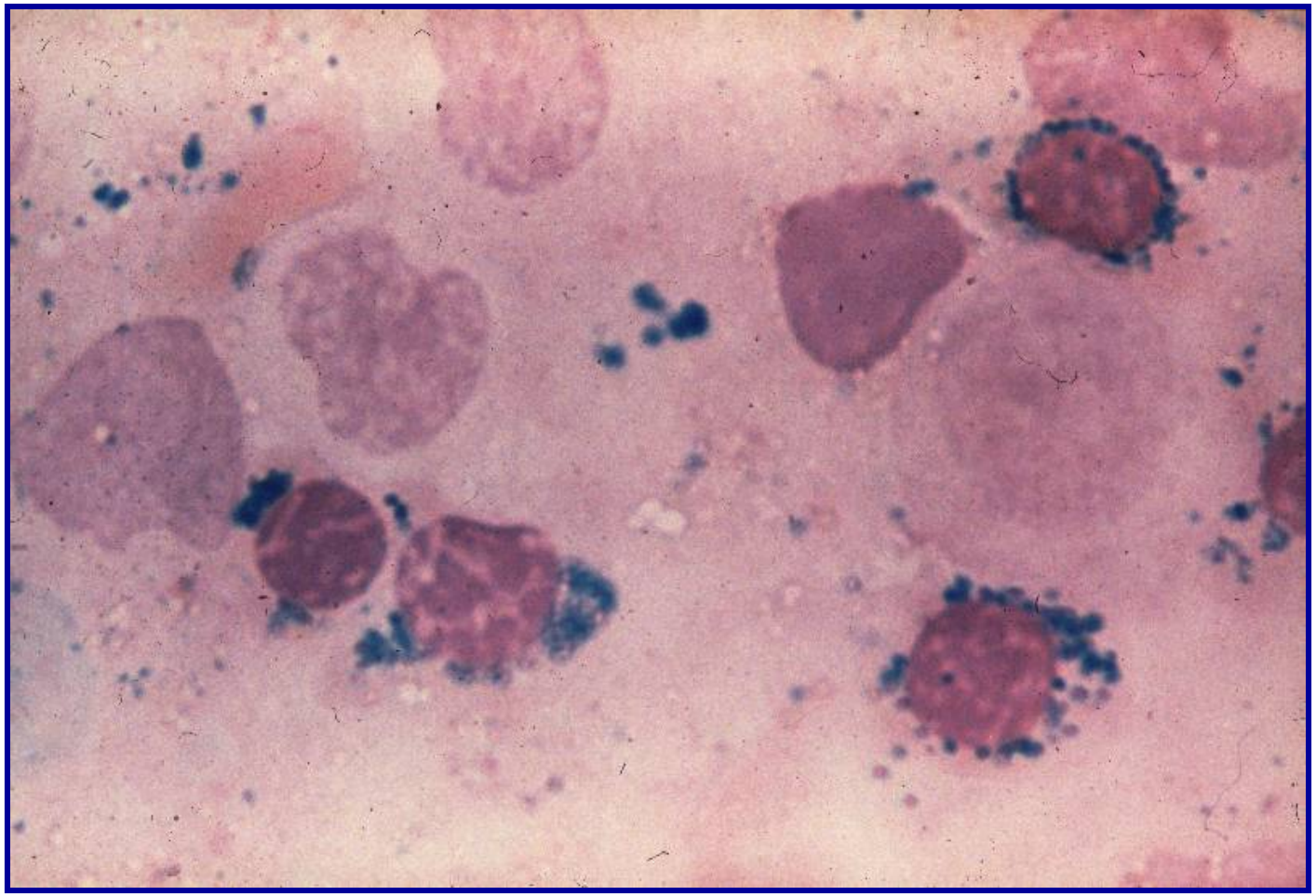
- Refractory anemia
- RA with ring sideroblast
- RA excess of blast
- Chronic myelomonocytic leukemia
- RA with excess of blast in transformation (RAEBT)

Figure 7. Refractory anemia with ringed sideroblasts (RARS)



Vardiman, J. W ASH Image Bank 2001;2001:100189

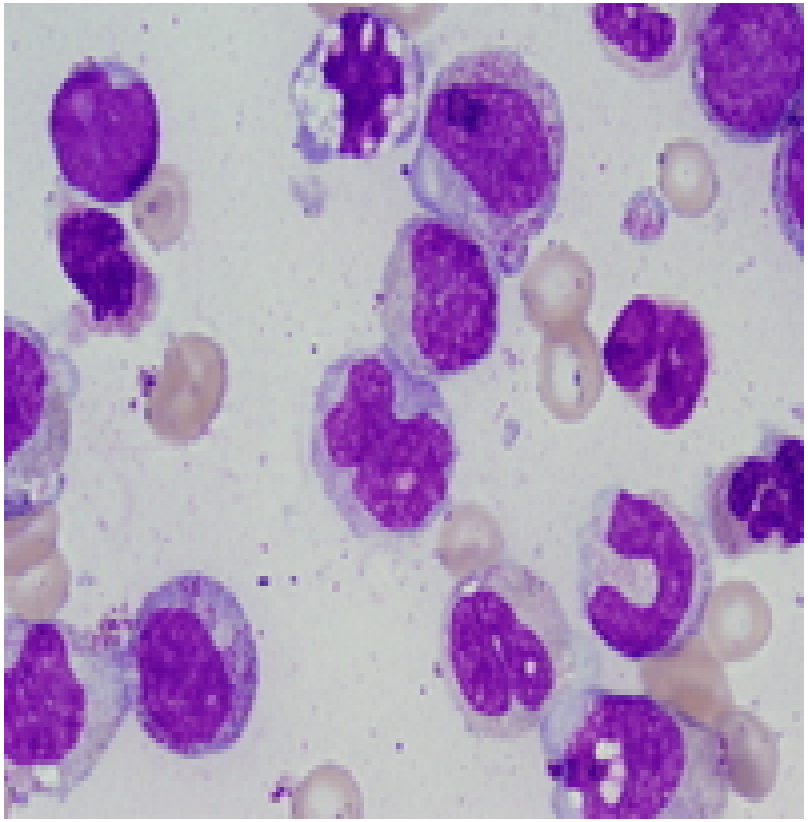
Ringed Sideroblasts

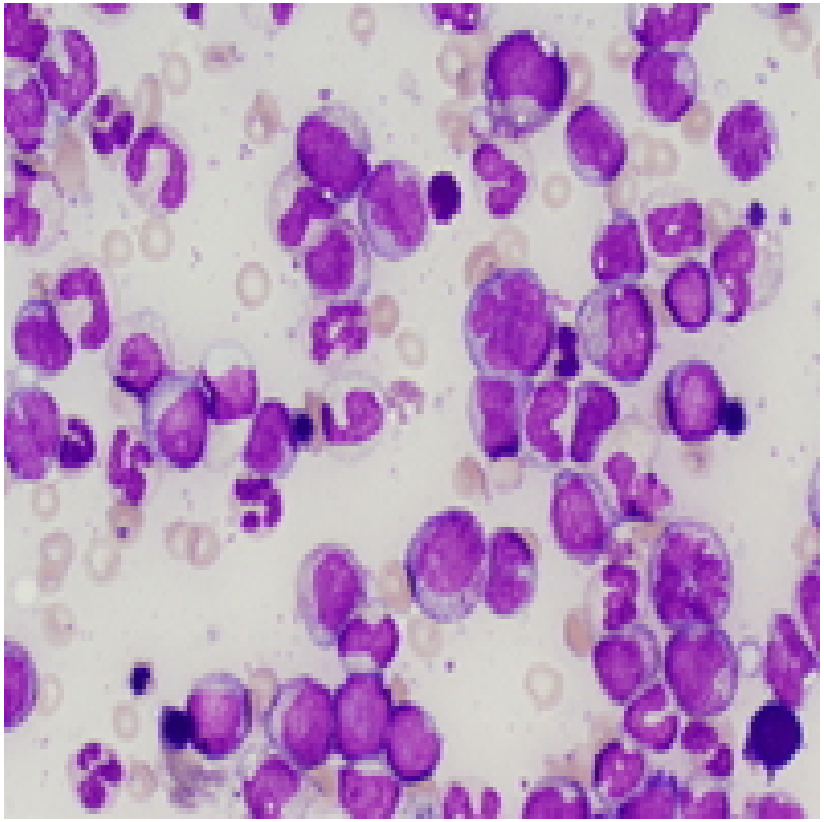


Chronic Myelomonocytic Leukemia (CMML)

- Chronic myelomonocytic leukemia (CMML) is a MDS/MPN characterized by the overproduction of maturing monocytic cells and sometimes dysplastic neutrophils, often accompanied by anemia and thrombocytopenia
- Overlap between MDS and MPD. FAB classification included as MDS. New classification mixed disorder.
- Cases of CMML have a peripheral blood monocyte count >1000/microL and often display other proliferative features such as splenomegaly, leukocytosis, and constitutional symptoms
- Prognosis is poor.

Chronic Myelomonocytic Leukemia





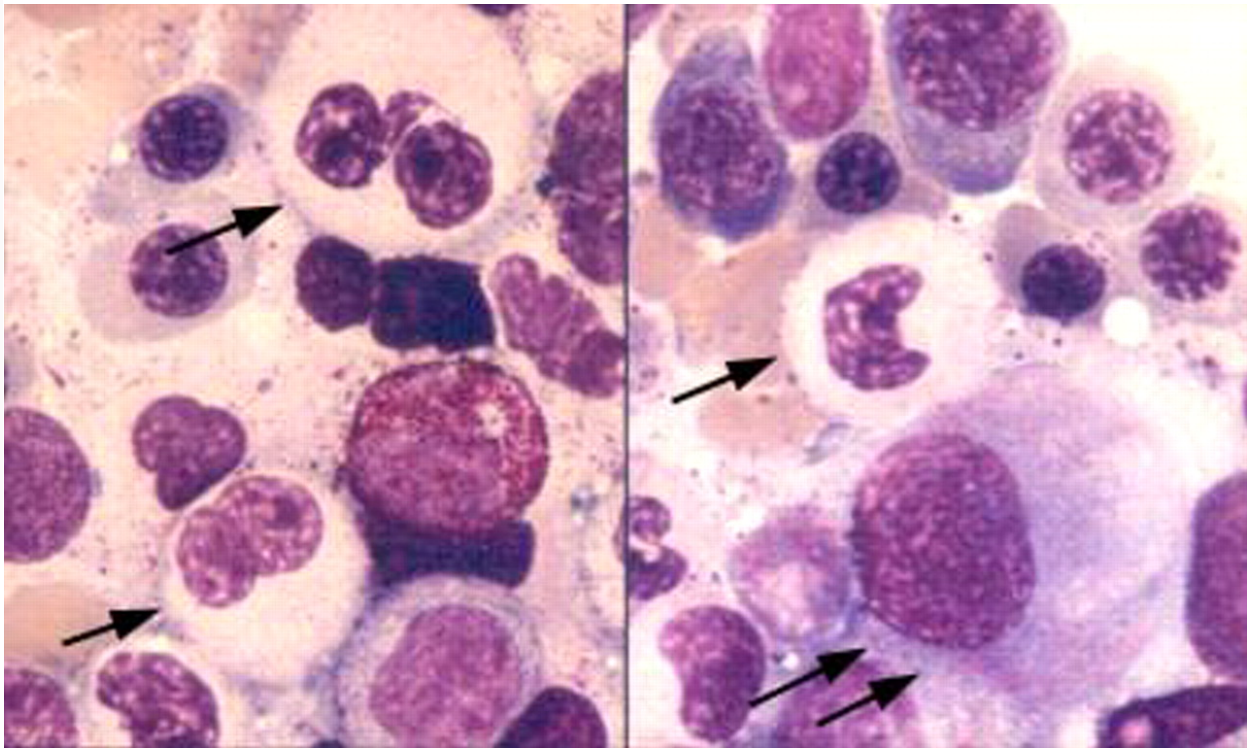
WHO Classification of MDS

- **Refractory Anemia**
- **RARS (one cell line affected vs more than one)**
- **Refractory anemia with multilineage dysplasia (RCMD)**
- **RAEB**
- **5q- syndrome**
- **Unclassifiable**

RELATION FAB & WHO

FAB	WHO
RefractoryAnemia (RA)	RA(unilineage) RCMD 5q-syndrome
RARS	RARS(unilineage) RCMD-RS
RAE-B (Blast)	RAEB-1 RAEB-2
RAEBt (Transformation)	AML e multilieage dys AML & MDS-TR
CMML	Myelodysplastic/ myeloproliferative disease

Figure 9. Refractory cytopenia with multilineage dysplasia (RCMD)



Vardiman, J. W ASH Image Bank 2001;2001:100188

Differential Diagnosis

- Several common diagnostic considerations given_these findings including:

- Causes of bone marrow failure(idiopathic or drug-induced aplasia)
- Hypersplenism
- Vitamin B12 or folate deficiency
- (PNH)– can have similar BM findings and MDS.

Prognosis of MDS

- Presence of blast indicate poor prognosis
- Uniformly fatal disorder due to infection and bleeding
- Chromosomal abnormalities are frequent including partial loss of chromosome 5, 7 and trisomy 8
- 5q- syndrome usually involve band q13 to q33 with anemia but no thrombocytopenia
- The International Prognostic Index (% blasts cells, cytogenetic and number of cytopenias)

Deletion of the long arm of chromosome 5 (5q- syndrome)

- Strongly associated with RA. Thrombocytosis.
- 5q- accounts for up to 70% of cytogenetic abnormalities in this subtype.
- The q arm of chromosome 5 is particularly rich in genes, which encoded haemopoietic growth factors and their receptors._For example , IL-3 , IL-4 , IL-5 , GM-CSF and the M-CSF receptor are located in this region.
- The potential for the loss of any or all of these genes contribute to the disruption of ordered haemopoiesis. This subtypes has a better prognosis.
- Better response to angiogenesis inhibitors: Lenalidomide

IPSS Score

Prediction of Survival
Prediction of AML

Survival and Acute Myelogenous Leukemia Evolution Score

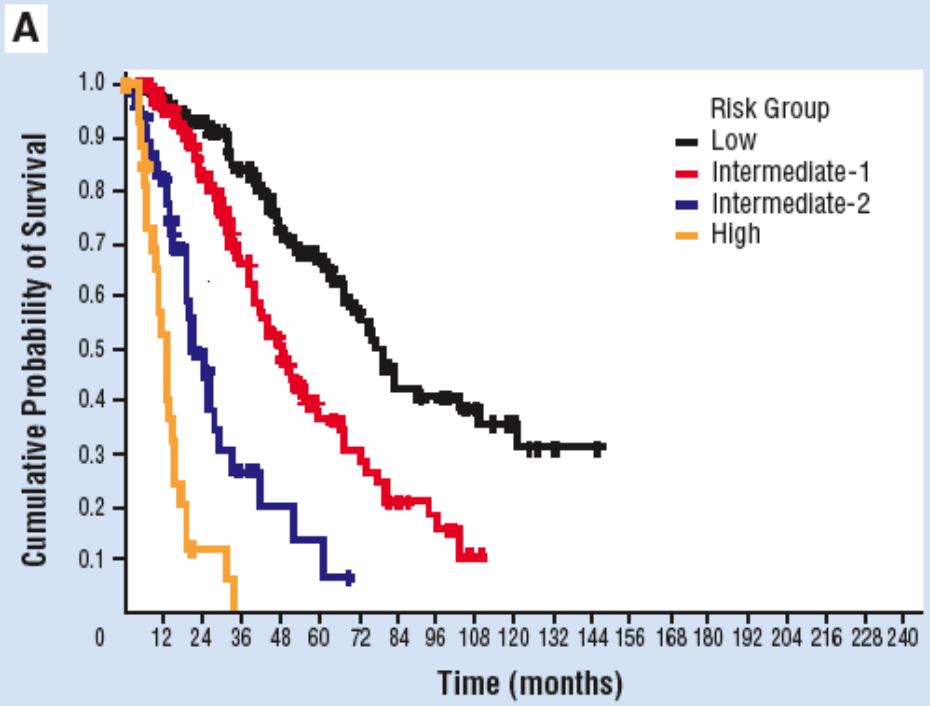
Prognostic variable	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5–10	—	11–20	21–30
Karyotype*	Good	Intermediate	Poor	—	—
Cytopenias**	0 or 1	2 or 3	—	—	—

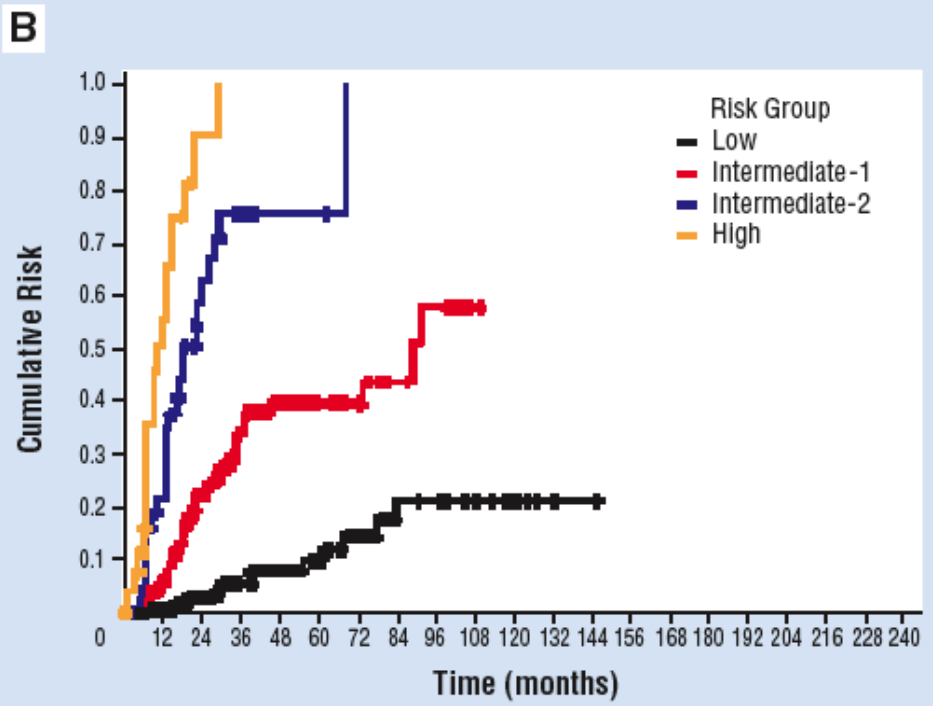
* Good = normal or any 1 of the following: –Y, del(5q), del(20q); Intermediate = other abnormalities; Poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.

** Cytopenias: neutrophil count < 1,500/μL, platelets < 100,000/μL, hemoglobin < 10 g/dL.

	IPSS Risk Category			
	Low	**Int-1**	**Int-2**	**High**
Combined score	0	0.5–1.0	1.5–2.0	≥ 2.5
Leukemic death	19%	30%	33%	45%
Median time to AML (yr)	9.4	3.3	1.1	0.2
Median survival (yr)*	5.7	3.5	1.2	0.4

Int-1 = intermediate-1, Int-2 = intermediate-2, AML = acute myelogenous leukemia. This research was originally published in Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89(6):2079-2088. Reprinted with permission.





Revised international prognostic scoring system (IPSS-R) in myelodysplastic syndrome

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/microL)	≥0.8	<0.8					

This scoring system was applied to an initial group of 7012 patients with primary MDS by the French-American-British classification who had at least two months of stable blood counts, ≤30 percent bone marrow blasts and ≤19 percent peripheral blood blasts, and who were observed until progression to AML transformation or death (did not receive disease-modifying agents for MDS). Patients could be stratified into five groups with the following estimated overall survival and progression to AML.

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25 percent AML evolution (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

The prognostic value of the IPSS-R was validated in an external cohort of 200 patients with MDS

AML: acute myeloid leukemia; MDS: myelodysplastic syndrome.
* Cytogenetic definitions:
Very good: -Y, del(11q).
Good: Normal, del(5q), del(12p), del(20q), double including del(5q).
Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones.
Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities.
Very poor: Complex: >3 abnormalities.
This research was originally published in Blood. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012.

Myelodysplastic syndrome (MDS) cytogenetic scoring system: International Prognostic Scoring System, Revised

Prognostic subgroups	Cytogenetic abnormalities	Percent of patients	Survival (years, median)	AML evolution, 25 percent (years, median)	Hazard ratio OS	Hazard ratio AML
Very good	–Y, del(11q)	4	5.4	NR	0.7	0.4
Good	Normal, del(5q), del(12p), del (20q), double including del(5q)	72	4.8	9.4	1	1
Intermediate	del(7q), +8, +19, i(17q), any other single or double, independent clones	13	2.7	2.5	1.5	1.8
Poor	–7, inv(3)/t (3q)/del(3q), double including –7/del(7q), complex: 3 abnormalities	4	1.5	1.7	2.3	2.3
Very poor	Complex: >3 abnormalities	7	0.7	0.7	3.8	3.6

AML: acute myeloid leukemia; OS: overall survival.

This research was originally published in Blood. Modified from: Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012; 120:2454-65.

The importance of indication of chromosomal abnormalities

- **To confirm diagnoses .**
- **To know the stage of disease.**
- **To know the direction of progression of disease.**
- **Multiple genetic abnormalities indicate late events in MDS.**

Pathogenesis of MDS

- Toxic exposure and genetic predisposition
- Immune response
- Hypermethylation and angiogenesis
- RAS mutation as a late effect
- Transformation

Treatment of MDS by risk stratification

- Supportive therapy
- ATG
- Hypomethylating agent: 5-Azacytidine and Dezacitidine
- Antiangiogenesis agents: Thalidomide and Lenalidomide
- Bone Marrow Transplantation is the only curative option

Supportive Care

- Transfusions
- Erythropoietin
- G-CSF
  - If no blasts

Bone Marrow Transplant

- Allogeneic hematopoetic stem-cell transplant
  - BMT can significantly prolong survival in patients with MDS
  - Approximately 1/3 of transplanted patients cured
- Significant morbidity and treatment related mortality
- Only 8-10% of all MDS patients eligible and have a donor (HLA-matched sibling)
  - Young patients (55 y/o or younger)

Therapeutic Goals When Transplant Not an Option

- **Consider natural history of the disease & patient preference**
- **Low or Intermediate-1 patients (IPSS): longer survival**
  - **Principle goal: amelioration of hematologic deficits**
  - **Need to be durable improvements**
- **Int-2/high risk patients:**
  - **Prolong survival is becomes more "immediate priority"**
  - **Allogeneic Transplantation can cure this disease and should be consider in this group of patients**

Targeting Angiogenesis in MDS

- Angiogenic molecules generated by the neoplastic clone
- Vascular endothelial growth factor-A (VEGF-A)
  - medullary neovascularity
  - clonal expansion of receptor-competent myeloblasts
  - Ineffective hematopoiesis in receptor naïve progenitors
- Inflammatory cytokines potentiate ineffective hematopoiesis
- Small molecule inhibitors of angiogenesis are a potential class of therapeutics
  - Thalidomide
  - Lenalidomide (Revlamid)

Other Therapeutic Targets: DNA methylation and Epigenetics

- Addition of a CH3 (methyl) group to a molecule (cytosine base)
  - **DNA methyltransferase**
- **Epigenetics**: Regulation of gene expression without altering DNA sequence
- Epigenetic silencing
  - Gene promoter regions get methylated
  - Leads to histone modifications
  - Chromatin is remodeled and becomes "invisible" to transcription factors
  - **Gene is "silenced"**
- Important role in embryogenesis
- Thought to be exploited by cancers to help express their malignant phenotype
  - silence tumor-suppressor genes

DNA Methylation Inhibitors

- 5-Azacytidine (AZA) and 5-aza-2'-deoxycytidine (DAC)
  - Cytosine analogs: inhibit DNA methylation by trapping DNA methyltransferases
    - Irreversible bond, degredaded
    - Cells then divide in absence of DNA methyltransferases
  - Dosage key
    - Hypomethylating at low doses, cytotoxic at high doses
    - Maximally tolerated dose (MTD) determined in 70's
- Sub-cutaneous injection daily X 7 days every 28 days
- FDA approval 2004 for treatment of MDS

Novel Therapies

- Nonmyeloablative Bone Marrow Transplantation or Reduced Intensity Regimens
- The development of less toxic and better tolerated nonmyeloablative or reduced intensity conditioning (RIC) regimens may allow allo-HCT to be performed in patients with MDS and advanced age or co-morbidity.
- The progression free survival for patients with MDS treated with standard allogeneic transplantation vs RIC was statistically similar.
- Others: Umbilical Cord Transplantation, Bortezomib and ATG/Cyclosporine

Conclusions

- MDS is a common hematological malignancy in the elderly
- Diagnostic criteria include morphological and specific chromosomal abnormalities.
- Classification of MDS include heterogeneous group of disorders with different cells lines affected and prognosis.
- Risk factors for prognosis of MDS help to select the treatment.
- Bone Marrow Transplantation is the only curative therapy for this disease, as should be consider in the high risk groups.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