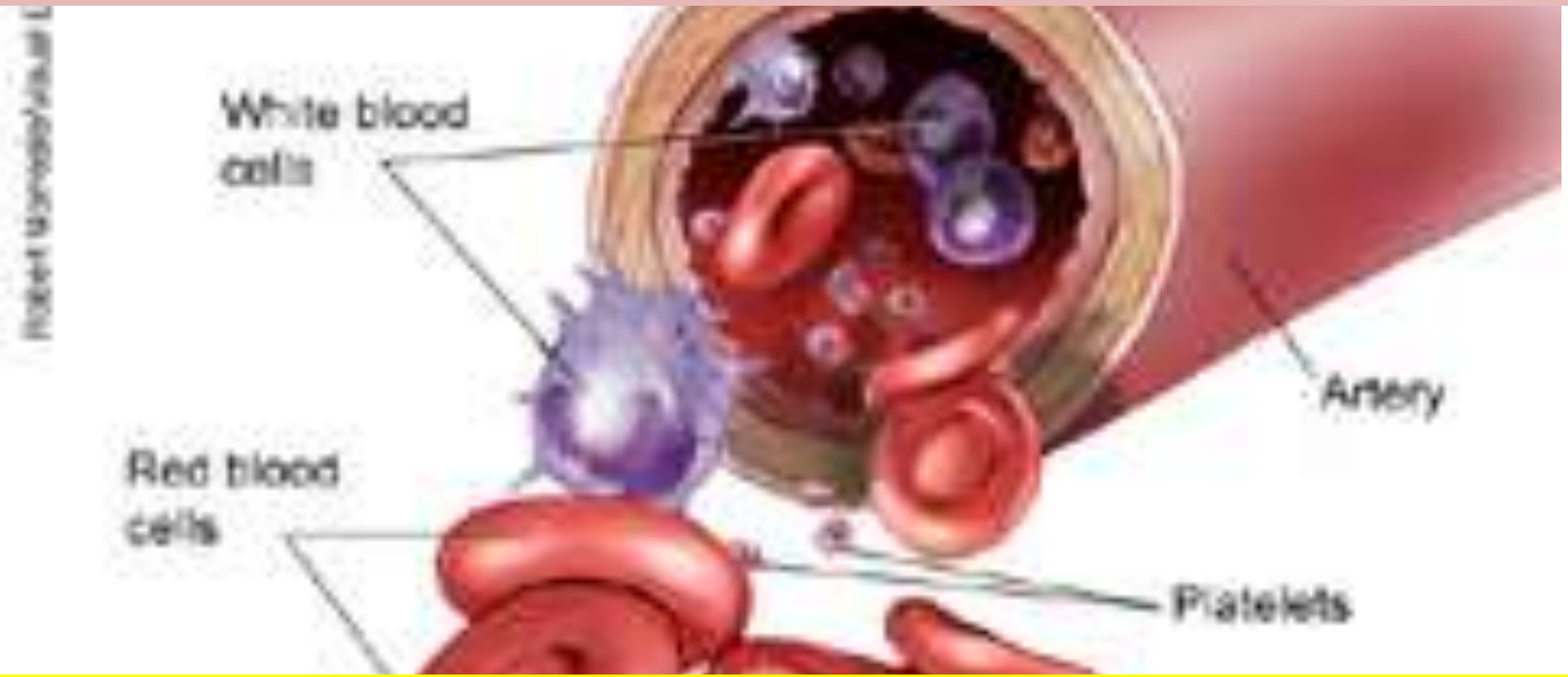
MYELODYSPLASTIC SYNDROMES (MYELODYSPLASIA)=MDS & Multiple Myeloma



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Medicine Faculty of Muhammadiyah Malang University
2023

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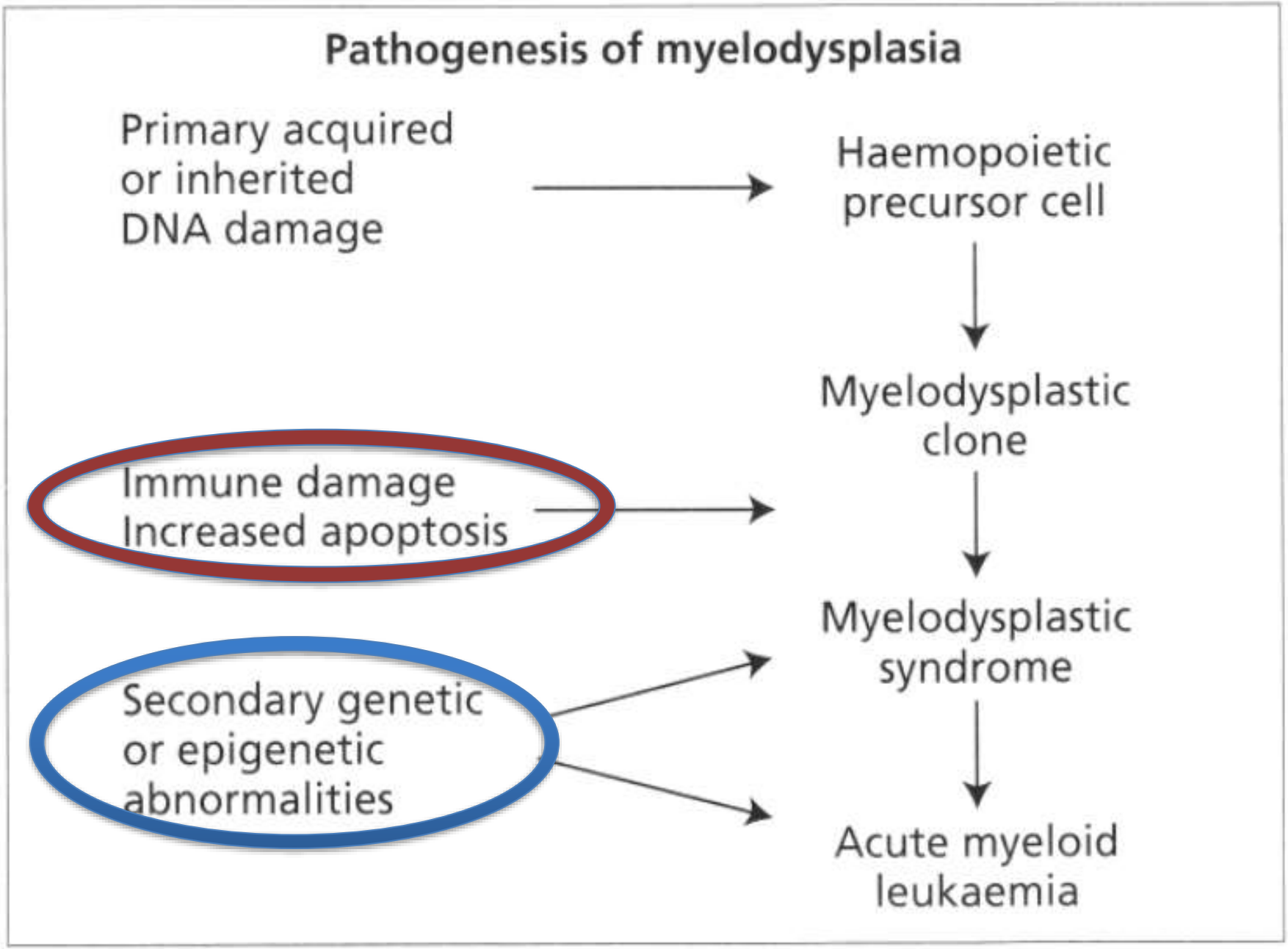
INTRODUCTION

- Group of clonal disorder of multipotent haematopoiesis stem cell (neoplastic disorder)
- MDS is heterogenous group of clonal disorders of bone marrow, differentiates ineffectivelly
- Their common feature is bone marrow failure→ ineffective haematopoiesis (reduced haematopoiesis activity)
- Predominantly a disease of the elderly
- The etiology of MDSs is not known (The association of increasing age suggests genetic damage caused by hazardous exposure or inherited susceptibility)
- Risk factors include exposure to benzene and other solvents, diesel fuel, smoking, and immunosuppression
- The pathophysiology of MDSs is complex and involves abnormalities in the regulation of cellular proliferation, maturation, and survival
- Prognosis is highly variable dependent on the subtype

Characteristic

- Myelodysplastic syndromes (MDS) are a group of diverse clonal hematopoietic disorders characterized by ineffective hematopoiesis
- Increasing bone marrow failure→ quantitative & qualitative abnormal all three myeloid cell line
- Hypercellular marrow & peripheral blood cytopenia
- Ineffective haematopoiesis (reduced haematopoiesis activity)
- **Dysplastic morphological abnormalities** form the basic for diagnosis
- Increased apoptosis within the marrow is common feature


Pathogenesis of myelodysplasia
Primary acquired or inherited DNA damage
Haemopoietic precursor cell
Myelodysplastic clone
Immune damage Increased apoptosis
Myelodysplastic syndrome
Secondary genetic or epigenetic abnormalities
Acute myeloid leukaemia

Approach to Diagnosis

Clinical Aspects

Symptoms

- Most frequent
  - Fatique, weakness and malaise due to anemia
- Less frequent
  - Infection due to the netropenia
  - Hemorrhage due to thrombocytopenia.
- Some individual are asymptomatic
  - Cytopenias identified in routine blood count
- Small percentage (rare)
  - Hepato- splenomegaly

Approach to Diagnosis

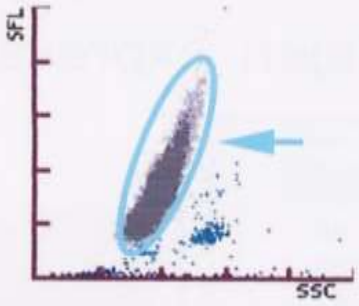
Laboratory diagnosis of MDS

- CBC + blood smear exam for dysplastic
- LDH
- BM aspiration (Romanowsky& Iron) and Biopsy
- BM Cytogenetic
- Flowcytometry (clinically indicated)
- Molecular (clinically indicated)→Next generation sequencing (NGS) has provided novel insights for the understanding of pathobiology of MDS, and yielded new markers related with diagnosis and prognosis
- Vit B12, Folate , SI-IBC,Feritin (clinically indicated)

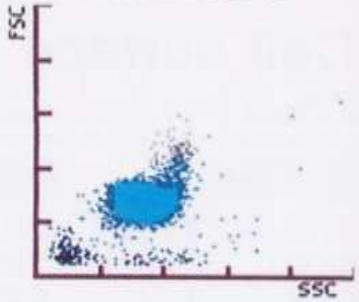
Complete blood count (CBC) test

WBC	52.39 *	[10^9/L]		
RBC	1.44 -	[10^{12}/L]		
HGB	47 -	[g/L]		
HCT	14.4 -	[%]		
MCV	100.0	[fL]		
MCH	32.6	[pg]		
MCHC	326	[g/L]		
PLT	55 *	[10^9/L]		
RDW-SD	51.5	[fL]		
RDW-CV	15.2	[%]		
PDW	9.6 *	[fL]		
MPV	9.0 *	[fL]		
P-LCR	17.3 *	[%]		
PCT	0.05 *	[%]		
NEUT	----	[10^9/L]	----	[%]
LYMPH	----	[10^9/L]	----	[%]
MONO	----	[10^9/L]	----	[%]
EO	0.01 *	[10^9/L]	0.0 *	[%]
BASO	0.08 *	[10^9/L]	0.2 *	[%]
RET	0.14	[%]	2.0	[10^9/L]
IRF	17.7	[%]		
LFR	82.3	[%]		
MFR	11.8	[%]		
HFR	5.9	[%]		

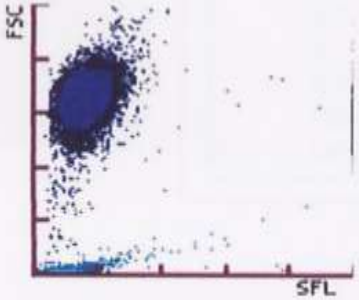
DIFF



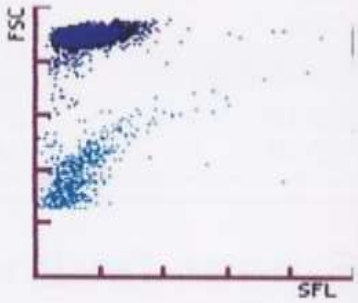
WBC/BASO



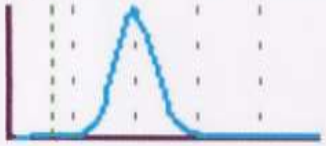
RET



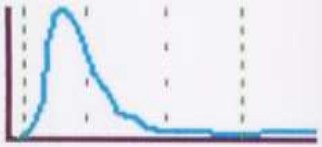
PLT-O



RBC



PLT



WBC IP Messages

WBC Abn Scattergram
Leukocytosis

Blasts?

RBC/RET IP Messages

Anemia

PLT IP Messages

Thrombocytopenia

PLT Clumps?

Visual count data

Stab	0 [%]
Seg	2 [%]
Lymph	4 [%]
Mono	0 [%]
Eo	0 [%]

Hematologic Finding

- Highly Variable
- Various combination of Cytopenias
  - Pancytopenia
  - Anemia in combination with neutropenia or thrombocytopenia
- Ineffective hematopoiesis, dyserythropoiesis, dysgranulopoiesis and dysmegakaryopoiesis
- Increased myeloblasts
- Normocellular or hypercellular BM
- Serum protein electrophoresis (SPEP or SPE) adalah tes laboratorium thp protein spesifik dalam darah (globulin)

Indikasi Pemeriksaan evaluasi darah tepi

Indikasi Klinis:

- Diagnaosis & monitoring penyakit hematologi
- Klinis mengarah→Sitosis (↑) atau sitopenia (↓) sel darah
- splenomegali, limfadenopati, atau gejala sistemik yang mengarah pada kelainan hematologi
- hiperleukositosis dengan kecurigaan ke arah leukemia
- limfositosis atau monositosis
- keganasan dengan kecurigaan metastasis ke sumsum tulang

Indikasi Laboratorium

- Konfirmasi kelainan kuantitatif hasil DL, atau terdapat perbedaan yang besar antara hasil saat ini dengan hasil sebelumnya
- Menindaklanjuti tanda peringatan dari alat hematologi otomatis, seperti: *blast, immature granulocyte, platelet clump, NRBC*, dll
- Ada tanda abnormal (tdk dpt terbaca) pd alat autoAnalizer terhadap Hitung jenis leukosit karena adanya sel muda

Pemeriksaan Gambaran Darah Tepi

- Informasi Update Laboratorium Medik-

Rumah Sakit Umum
UNIVERSITAS
MUHAMMADIYAH
M A L A N G

Layananku Pengabdian

INSTALASI LABORATORIU

Dokter Laboratorium : dr.Diah Hermayanti,Sp.PK, Dr.dr. Sulistyo Mulyo Agustini,Sp.PK

NamaPasien	:	Tanggal	: Juli 2020
Umur	: Thn	Dokter	: ARDHI BUSTAMI, SpPD
Alamat	:	Kelas/Ruang	:
Telp	:-	Penjamin	: Umum
Bahan Pemeriksaan	: Darah		
Bahan diterima tanggal			

EVALUASI HAPUSAN DARAH TEPI

ERITROSIT :
LEKOSIT :

Eo / bas / stab / seg / lim /mo =

TROMBOSIT :

KESIMPULAN :
SARAN :

Pemeriksa,

Dr.dr. Sulistyo Mulyo Agustini, SpPK

Jl. Raya Tlogomas No. 45 Desa Landungsari, Kec. Dau, Kab. Malang - Jawa Timur 65144
Telp. : 0341-561666
Email : hospital@umm.ac.id

Hematologic Finding

- Most common example

  normo or hypercellular BM with

  ineffective erythropoiesis , erythroid hyperplasia

  anemia with reticulocytopenia

Classification
The French American British (FAB) & WHO

type	Pheripheral blood	Bone marrow	Approximated survival (months)
Refractory anaemia (RA)	Blast < 1%	Blast < 5 %	50
RA with ring sideroblasts (RARS)	Blast <1 %	Blast <5 % ring sideroblast > 15 % of total erytroblast	50
RA with excess blasts (RAEB)	Blast < 5 %	Blast 5 – 20 %	11
RAEB in transformation (RAEB-t)	Blast > 5 %	Blast 20-30 % or Auer rods present	5
Chronic myelomonocytic leukemia (CMML)	As any of the above 10 x 106/l monocytes	As any of the above promonocytes	11

Morphological manifestations of dysplasia in MDS

DYSERYTHROPOIESI

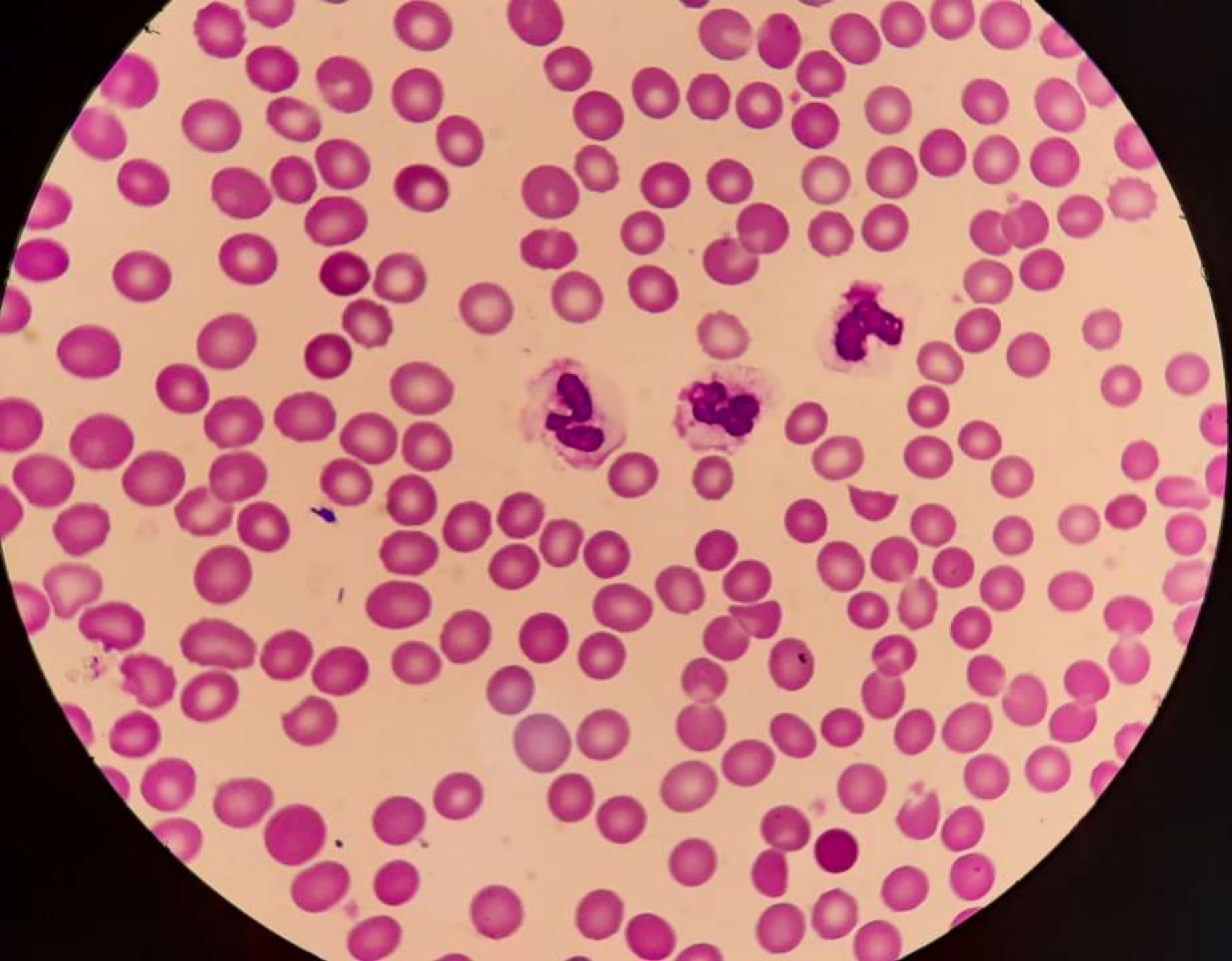
- Nuclear budding
- Internuclear bridging
- Karyorrhexis
- Multinuclearity
- Megaloblastoid changes
- Ring sideroblasts
- Vacuolization
- Periodic acid-Schiff (PAS) positivity

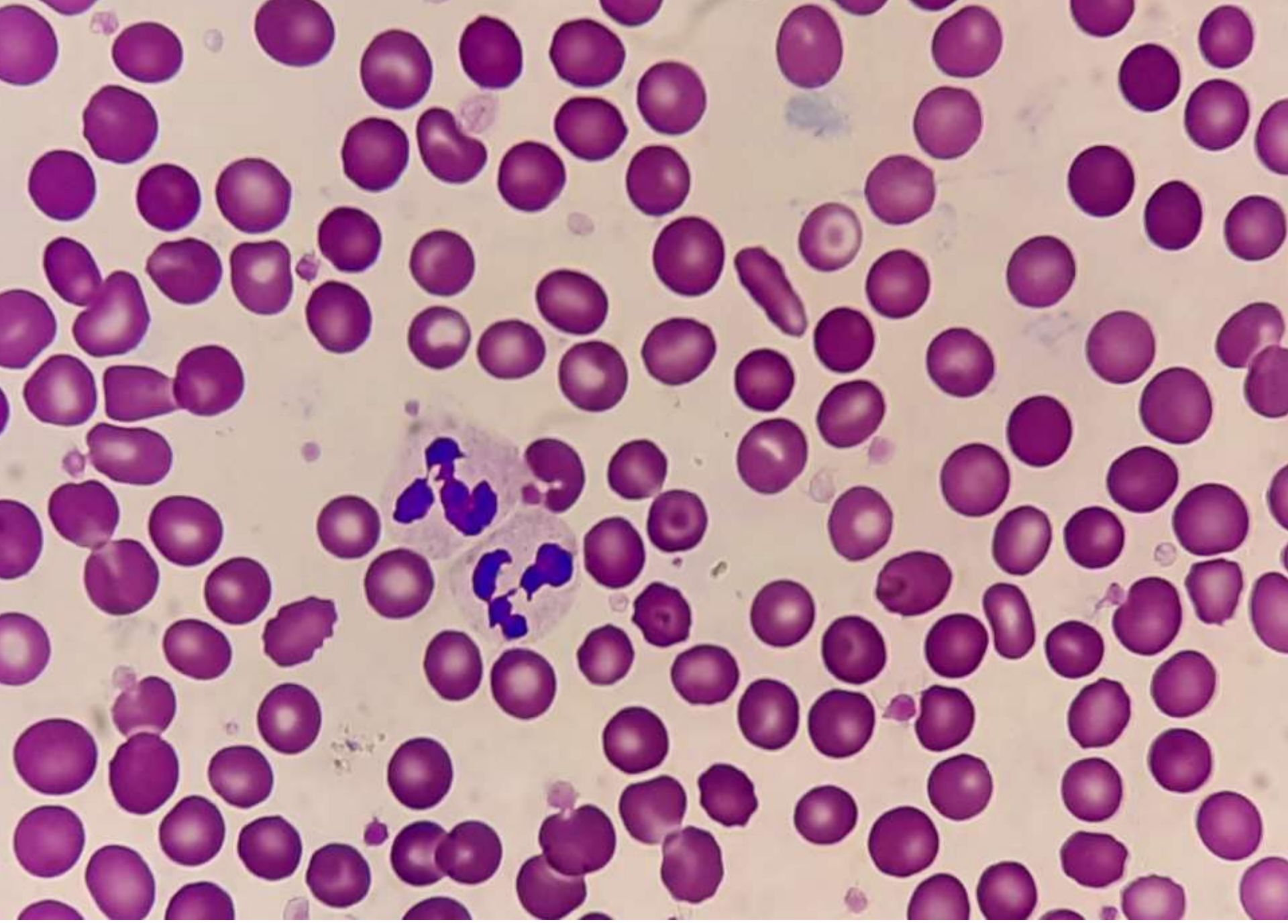
DYSMYELOPOIESIS

- Small / unusually large size
- Nuclear hyposegmentation (pseudo-Pelger-Huet)
- Nuclear hypersegmentation
- Decreased granules; agranularity
- Pseudo-Chediak-Higashi granules
- Dohle bodies
- Auer rods

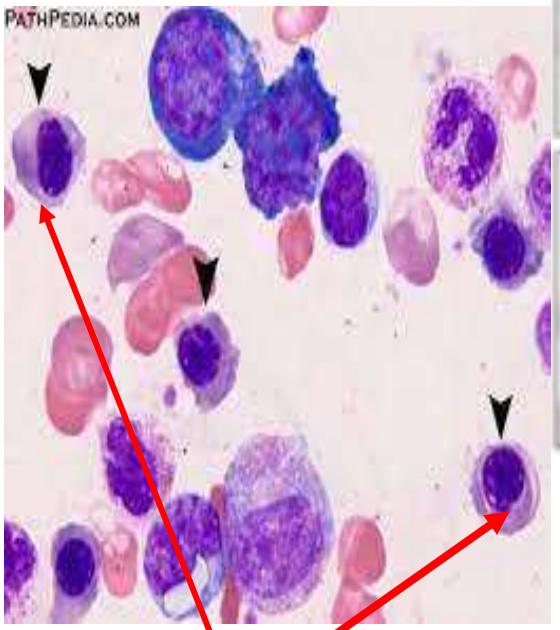
DYSMEGAKARYOPOIESIS

- Micromegakaryocytes
- Nuclear hypolobation
- Multinucleation

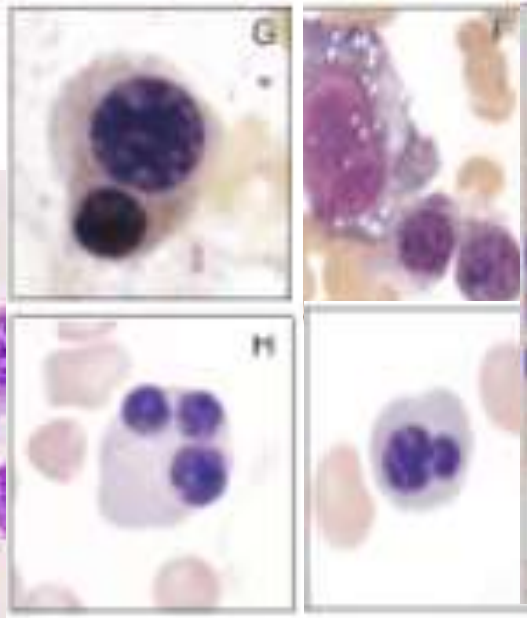


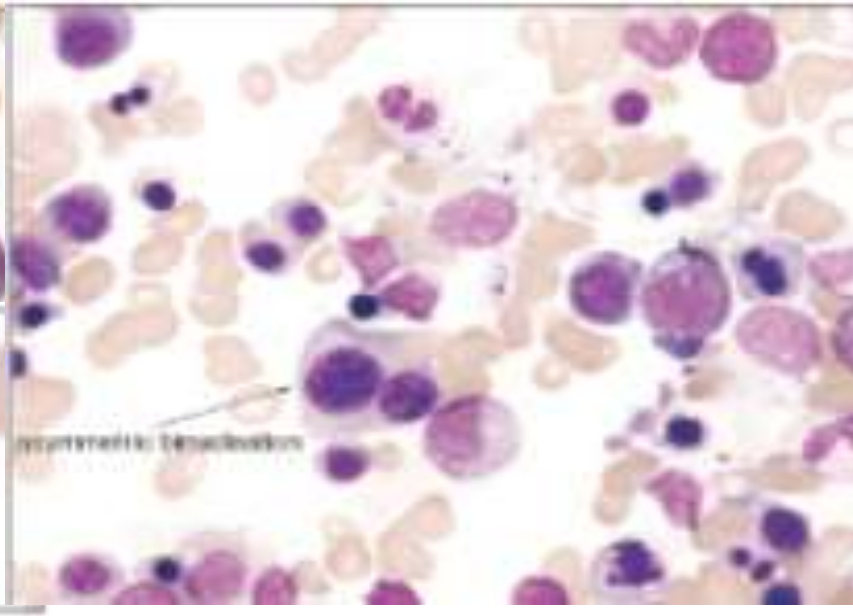


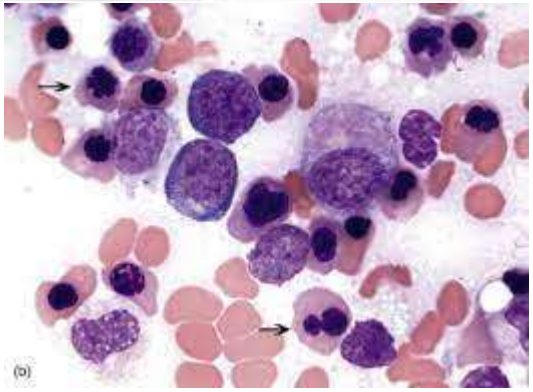
Dyserythropoiesis



sideroblast erythroid precursors







PelgerHuet

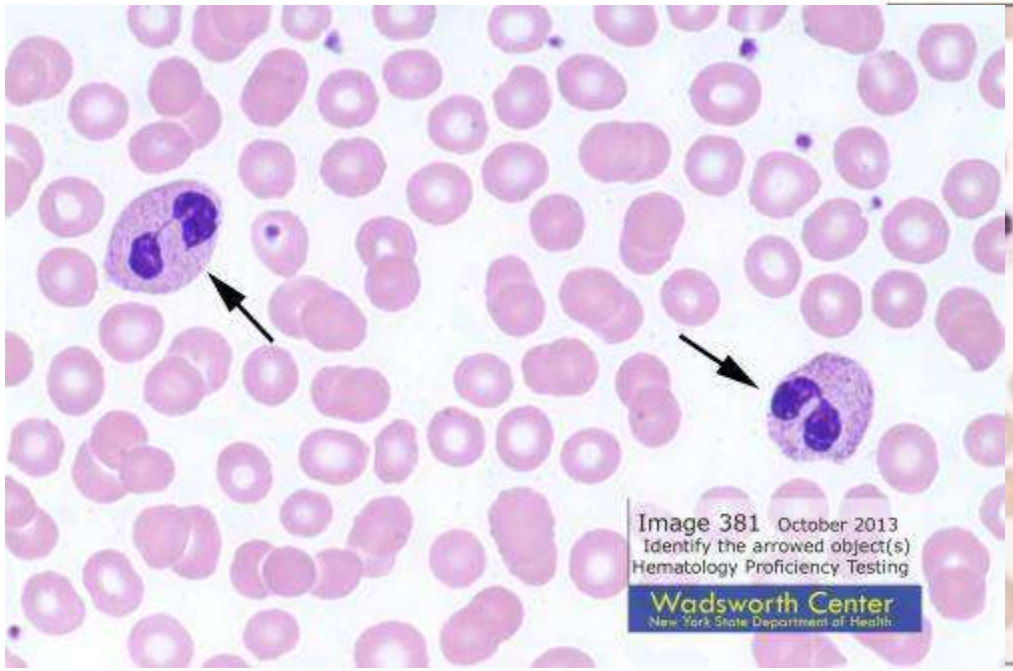
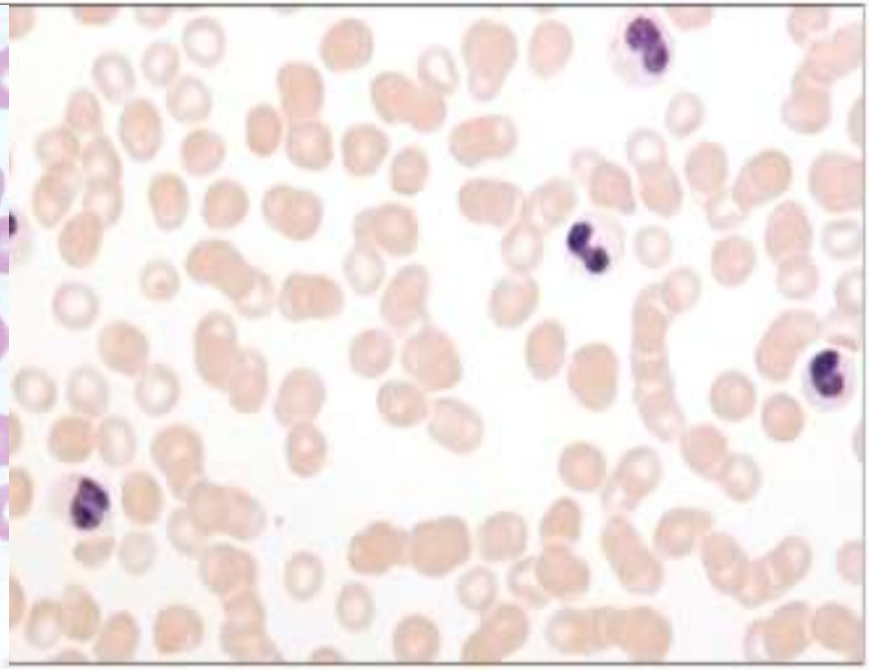
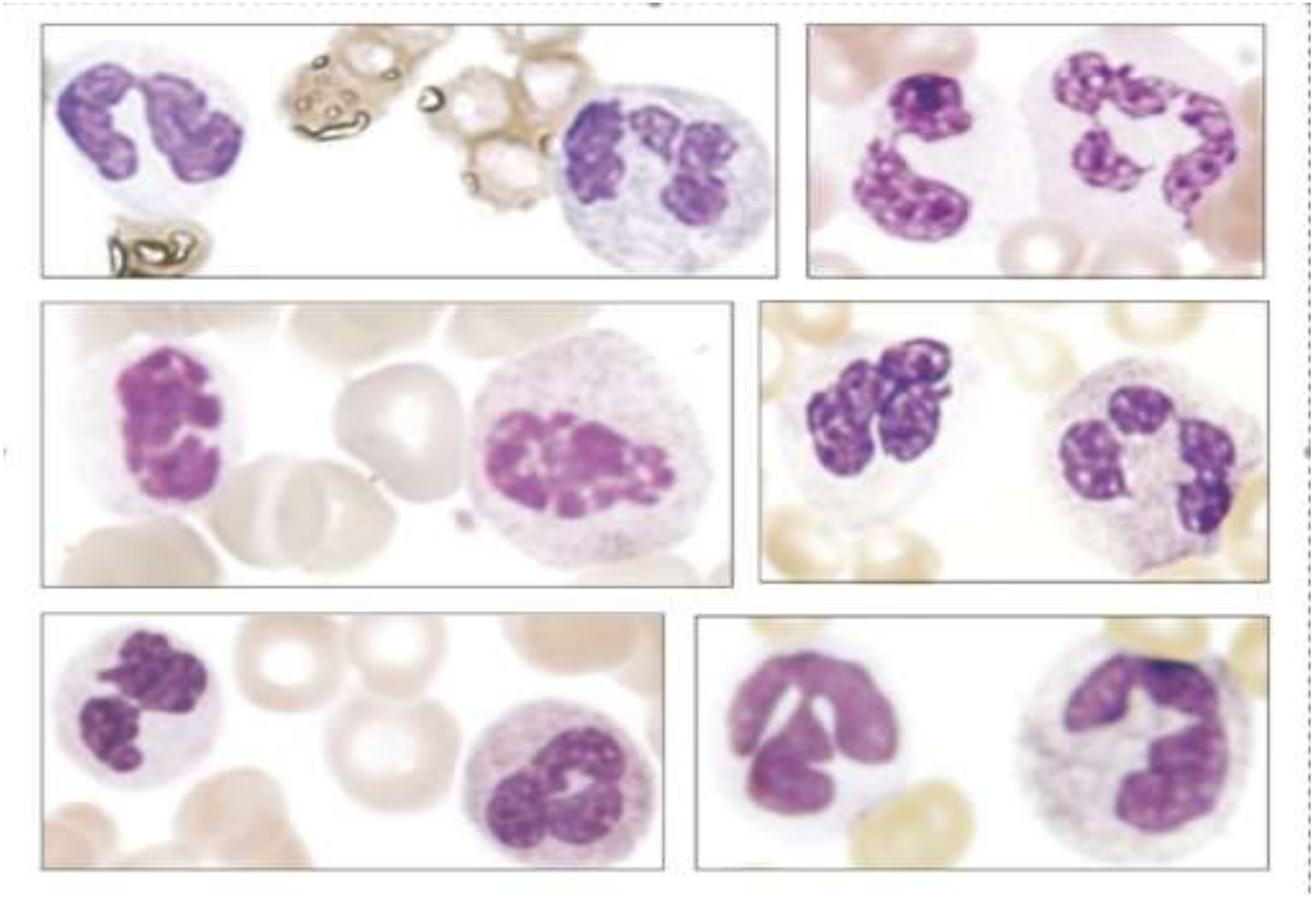


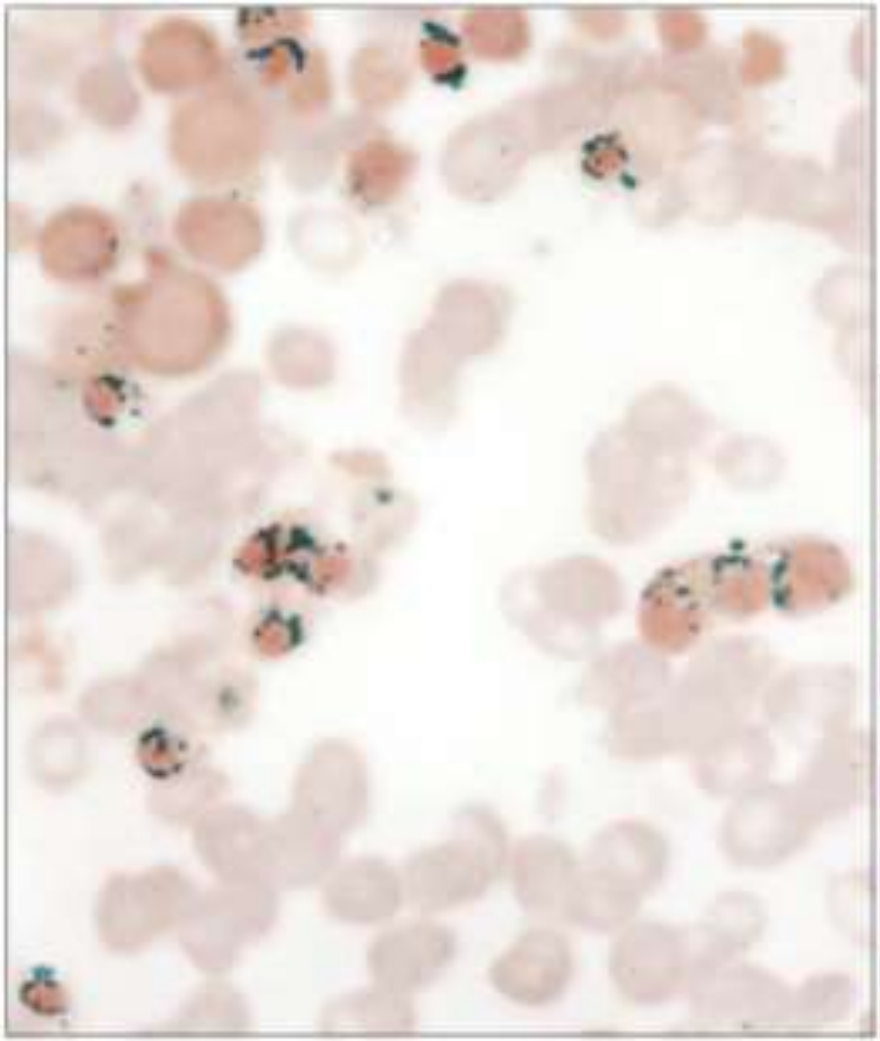
Image 381 October 2013
Identify the arrowed object(s)
Hematology Proficiency Testing
Wadsworth Center
New York State Department of Health

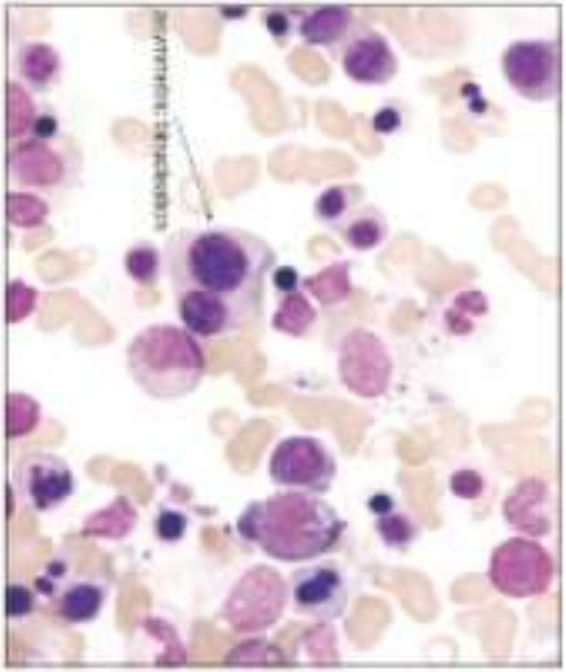


Dysgranulopoiesis

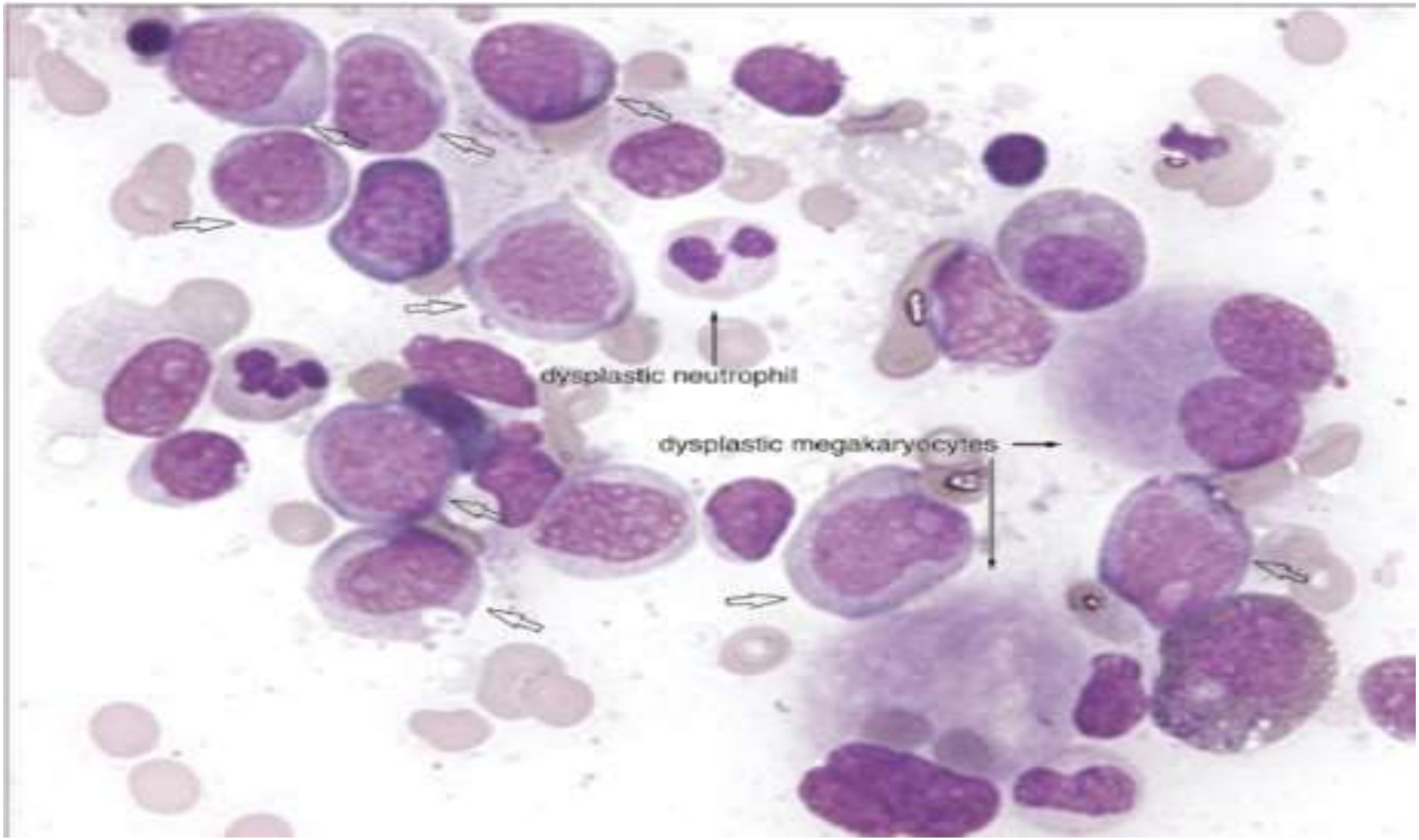


RARS

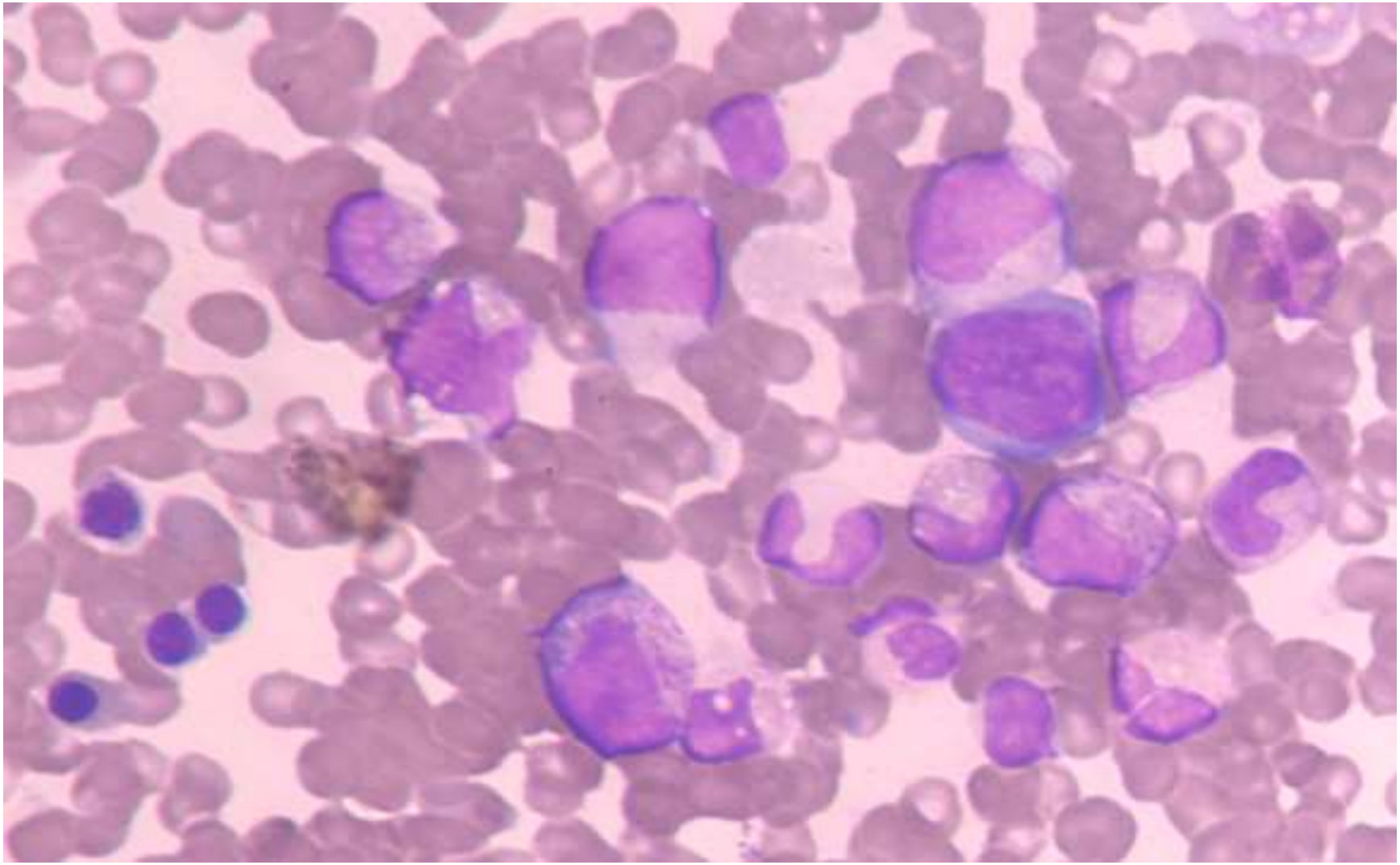




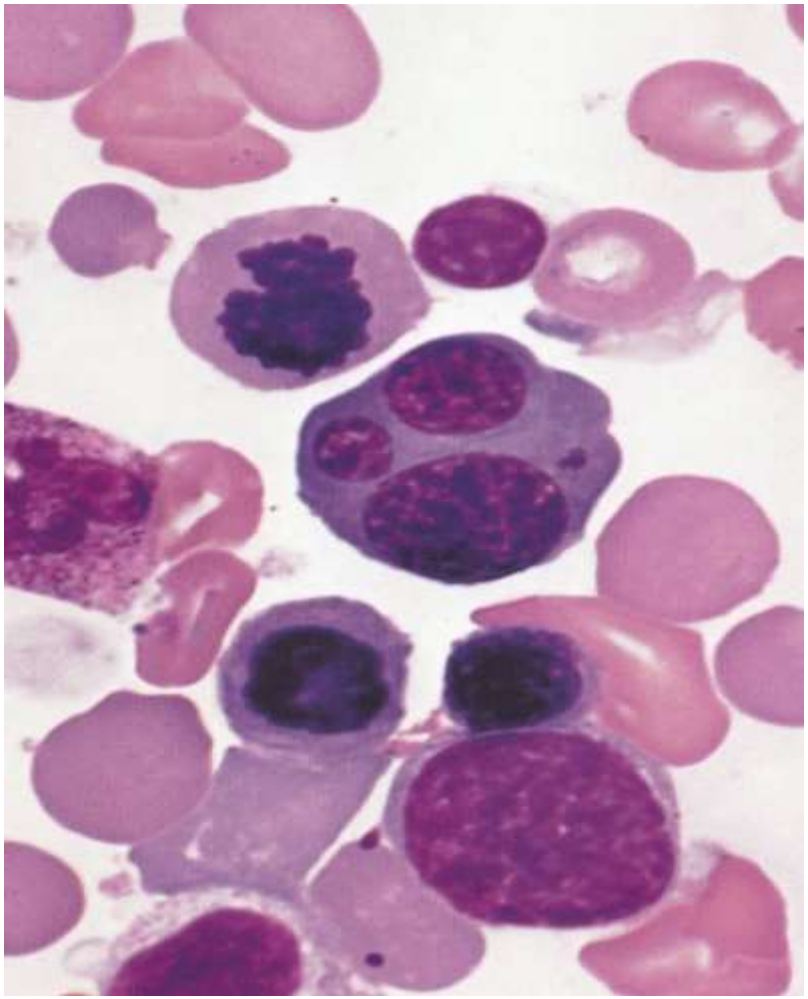
RAEB

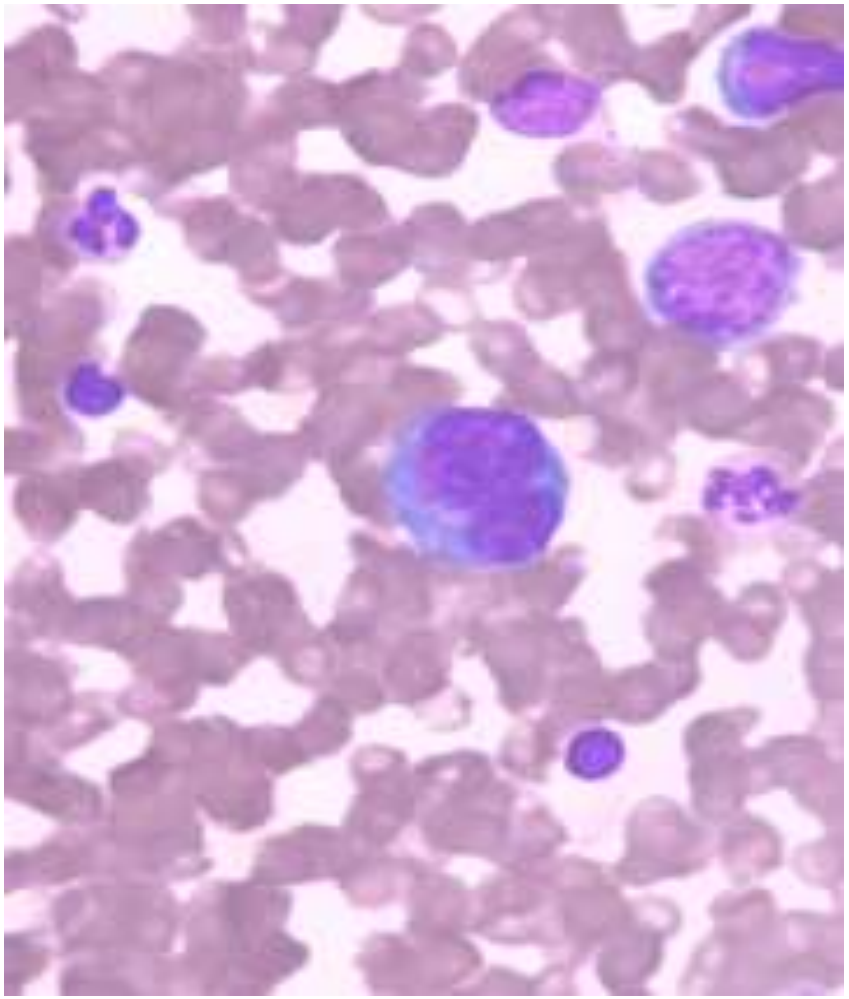


RAEB



Dyserythropoiesis

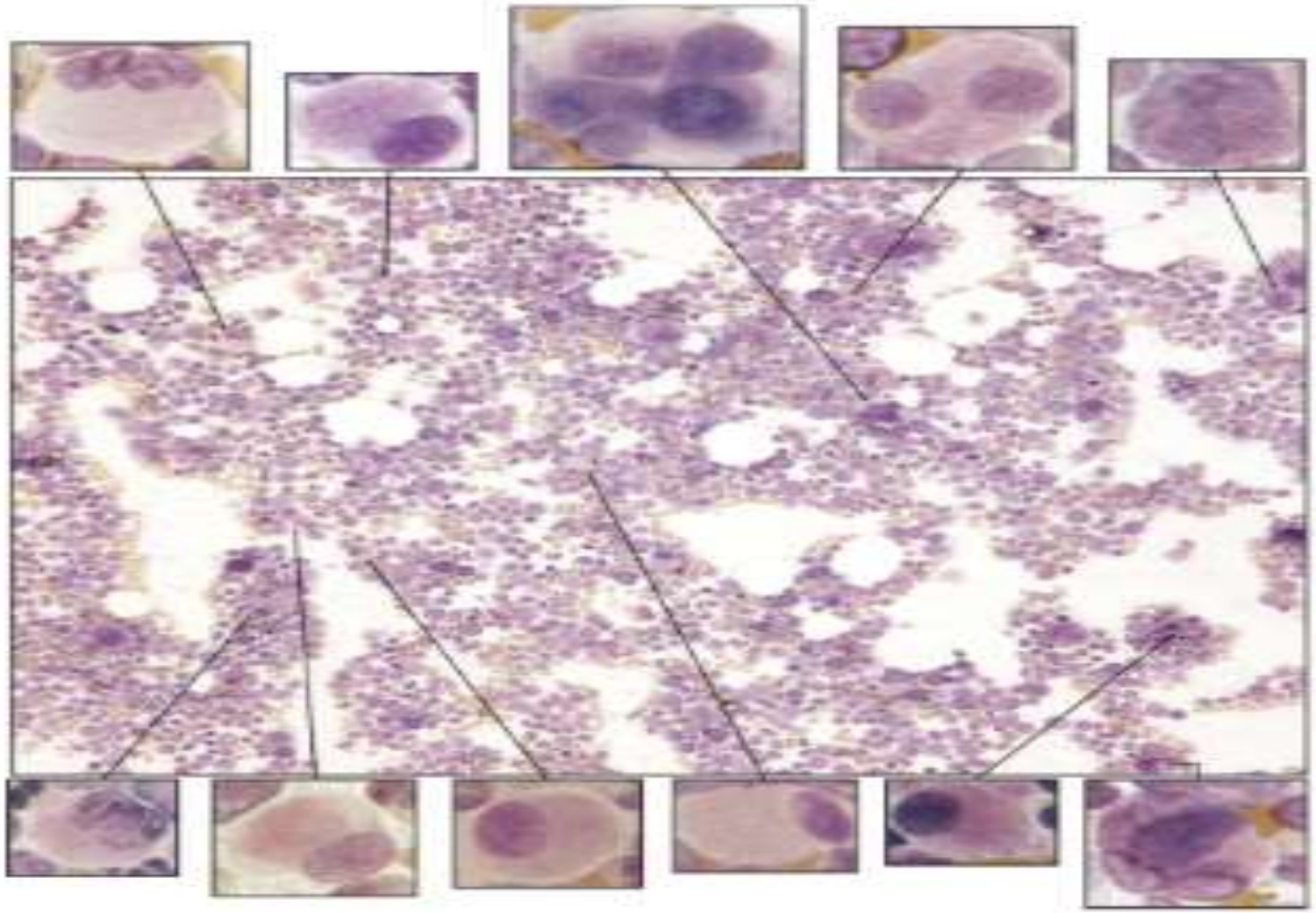




International Prognostic Scoring System

- Patients with 20-30 % blasts may be considered as MDS or AML.
- Cytopenias:
  - neutrophil count <1,800/mcL, platelets < 100,000/mcL, Hb< 10g/dL.
- Cytogenetics:
  - Good = normal, -Y alone, del(5q) alone, del(20q) alone;
  - Poor = complex (3 abnormalities) or chromosome 7 anomalies;
  - Intermediate = other abnormalities. [This excludes karyotypes t(8;21), inv16, and t(15;17), which are considered to be AML not MDS.] [3]

Dysmegakaryopoiesis



Prognostic Factors in MDS

- Clinical
  - Therapy related MDS
- Blood
  - Severe cytopenias
  - Raised LDH & Beta 2 microglobulin
- Marrow
  - Increased Blast
  - Trilineage Dysplasia
- Chromosome abnormalities
  - Loss of chromosome 5 or 7
  - Deletion of chromosome 3q,5q (excluding 5q syndrome),7q,17 p
  - Structural abnormality of chromosome 11q 23

Myelodysplastic Syndromes

Guidelines Index
MDS Table of Contents
Discussion, References

CLASSIFICATION SYSTEMS FOR DE NOVO MDS (page 1 of 2)

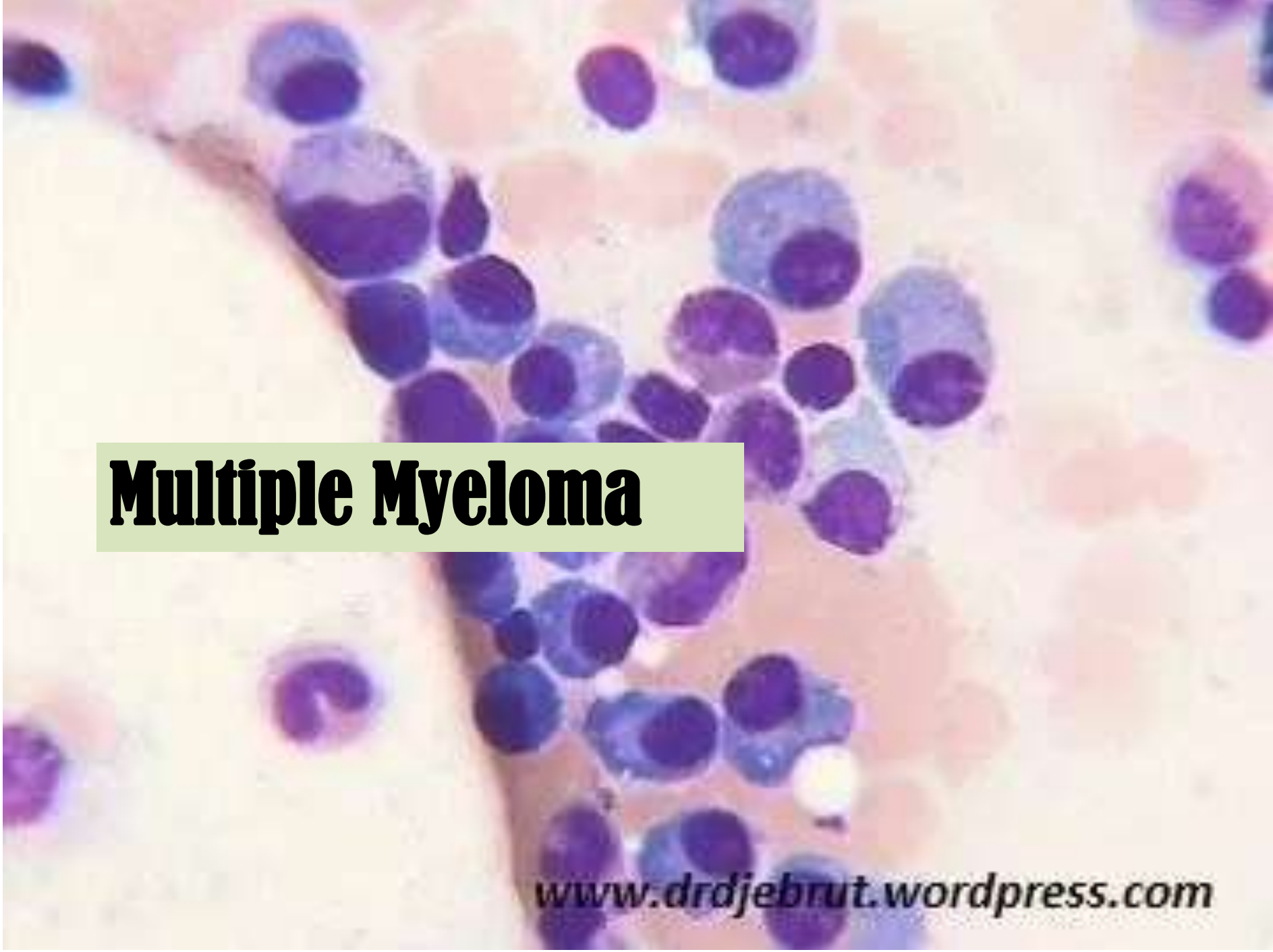
FAB Classification of MDS[f,g]

FAB subtype	% of Peripheral blasts	% of Bone marrow blasts
Refractory anemia (RA)	< 1	< 5
Refractory anemia with ringed sideroblasts (RARS)	< 1	< 5
Refractory anemia with excess blasts (RAEB)	< 5	5-20
Refractory anemia with excess blasts in transformation (RAEB-t)	≥ 5	21-30
Chronic myelomonocytic leukemia (CMML) (> 1,000 monocytes/mcL blood)	< 5	5-20

WHO Classification of MDS[h,i]

Subtype	Blood	Bone marrow
Refractory anemia (RA)	Anemia; no or rare blasts	Erythroid dysplasia only; < 5% blasts; < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia); no or rare blasts; no Auer rods; < 1x 10^9/L monocytes	Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines; < 5% blasts; no Auer rods; < 15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia; no blasts	Erythroid dysplasia only; < 5 % blasts; ≥ 15 % ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia); no or rare blasts; no Auer rods; < 1 x 10^9/L monocytes	Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines; < 5% blasts; no Auer rods; ≥ 15 % ringed sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias; < 5% blasts; no Auer rods; < 1 x 10^9/L monocytes	Unilineage or multilineage dysplasia; 5% to 9% blasts; no Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias; 5-19% blasts; Auer rods ±; < 1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts; Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias; no or rare blasts; no Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes; < 5% blasts; no Auer rods
MDS associated with isolated del(5q)	Anemia; < 5% blasts; platelets normal or increased	Normal to increased megakaryocytes with hypolobated nuclei; < 5% blasts; no Auer rods; isolated del (5q)

[f] FAB = French American British classification system of MDS


Multiple Myeloma
www.drdjebrut.wordpress.com

Multiple Myeloma

- Myeloma can have different features in each patient
- Multiple myeloma is a clonal plasma cell proliferative disorder characterized by the abnormal increase of monoclonal immunoglobulins
- the excess production of these plasma cells can ultimately lead to specific end-organ damage
- clinical manifestations are present: hypercalcemia, renal dysfunction, anemia, or bone pain accompanied by lytic lesions
- Ciri khas dari penyakit ***multiple myeloma*** (MM) adalah adanya protein M (komponen M, protein myeloma)
- kadar total protein 12,3 g/dl (N=6-8,5 g/dl), albumin 3,64 g/dl (N=3,5-5,5), dan globulin 8,66 g/dl (2,5-4,5 g/dl).
- elektroforesis protein→ protein monoclonal (fraksi gamma globulin) Sumber: *Wintrobe's Clinical Hematology 12th edition*

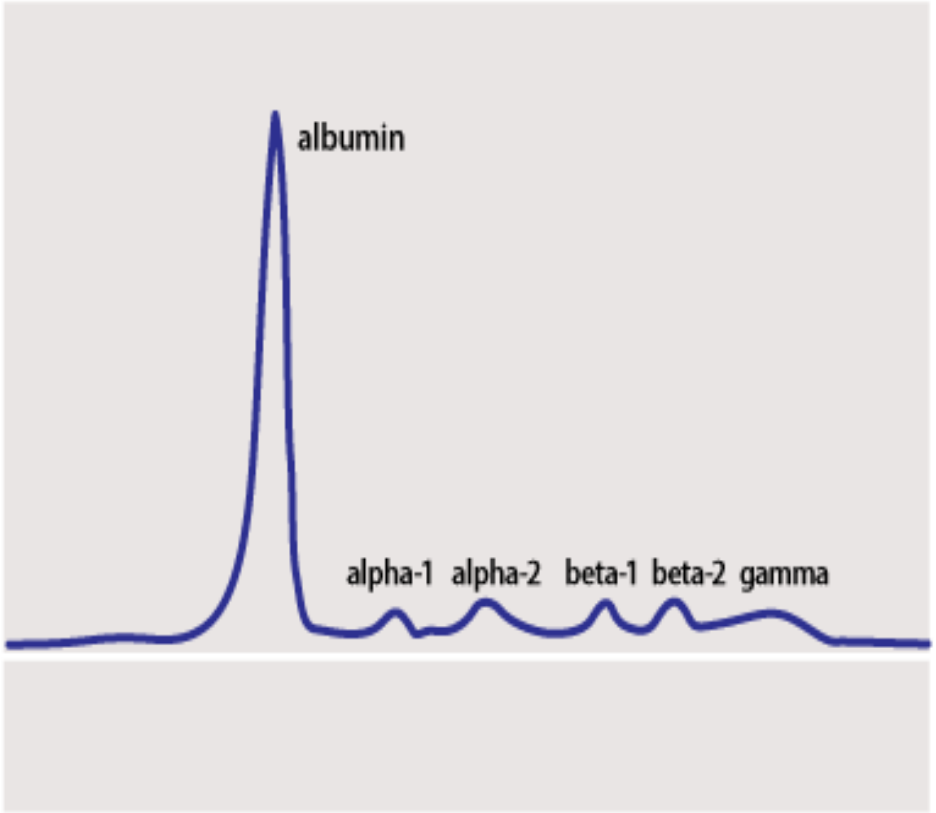
Laboratory Diagnosis of Multiple Myeloma

- Laboratory tests (blood)→Complete blood count (CBC) assesses the presence or absence of anemia (low red blood cell count), low white blood cell count, and low platelet count.
- Urine protein electrophoresis (UPEP)
- Chemistry/Metabolic Panel is particularly important for assessing kidney function (creatinine and BUN), albumin, calcium level, and LDH. C-reaction Protein
- Serum Protein Electrophoresis (SPEP) assesses the amount of abnormal (monoclonal) protein, but does not identify its type.
- Immunofixation electrophoresis demonstrates the type of myeloma protein; i.e., heavy chain (G, A, D, or E); or light chain (kappa or lambda), but does not quantify it.
- Genetic studies (done on biopsy specimens)

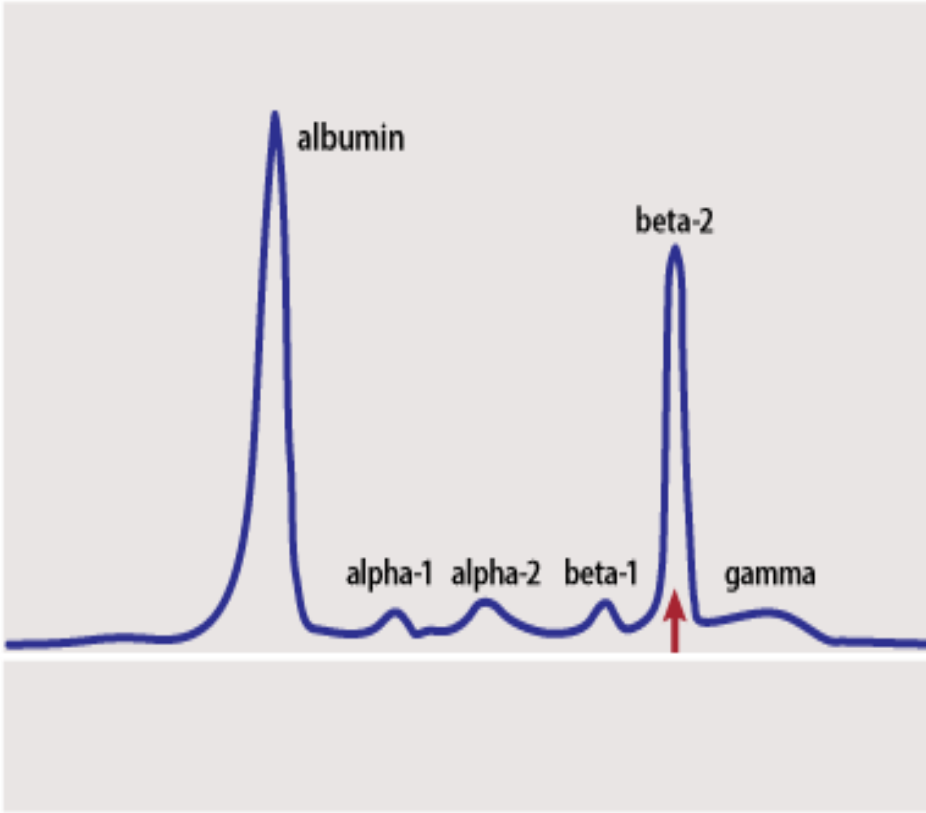
Lab findings

- Anemia, leukopenia, thrombocytopenia
- ⇩ALb, reversed A:G ratio
- ⇧serum creat, uric acid, urea
- Abnormal coagulation
- ⇧Serum Ca
- Proteinuria and cast
- ⇧ESR
- LOW NORMAL ALKALINE PHOSPHATASE
- Red cells show rouleaux formation
- BENCE-JONES PROTEIN in urine in 30%

SPEP Test Results

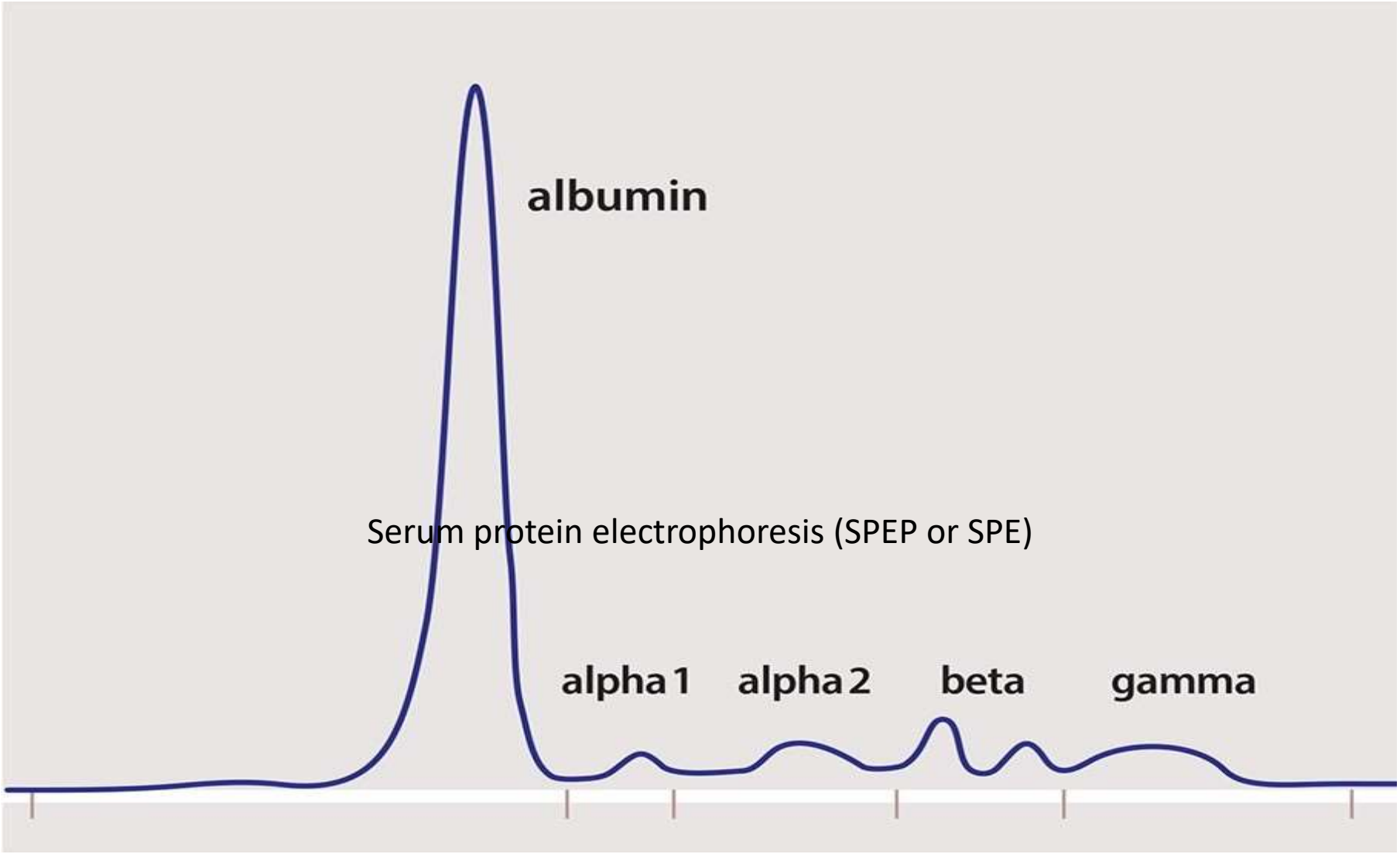


Normal SPEP result



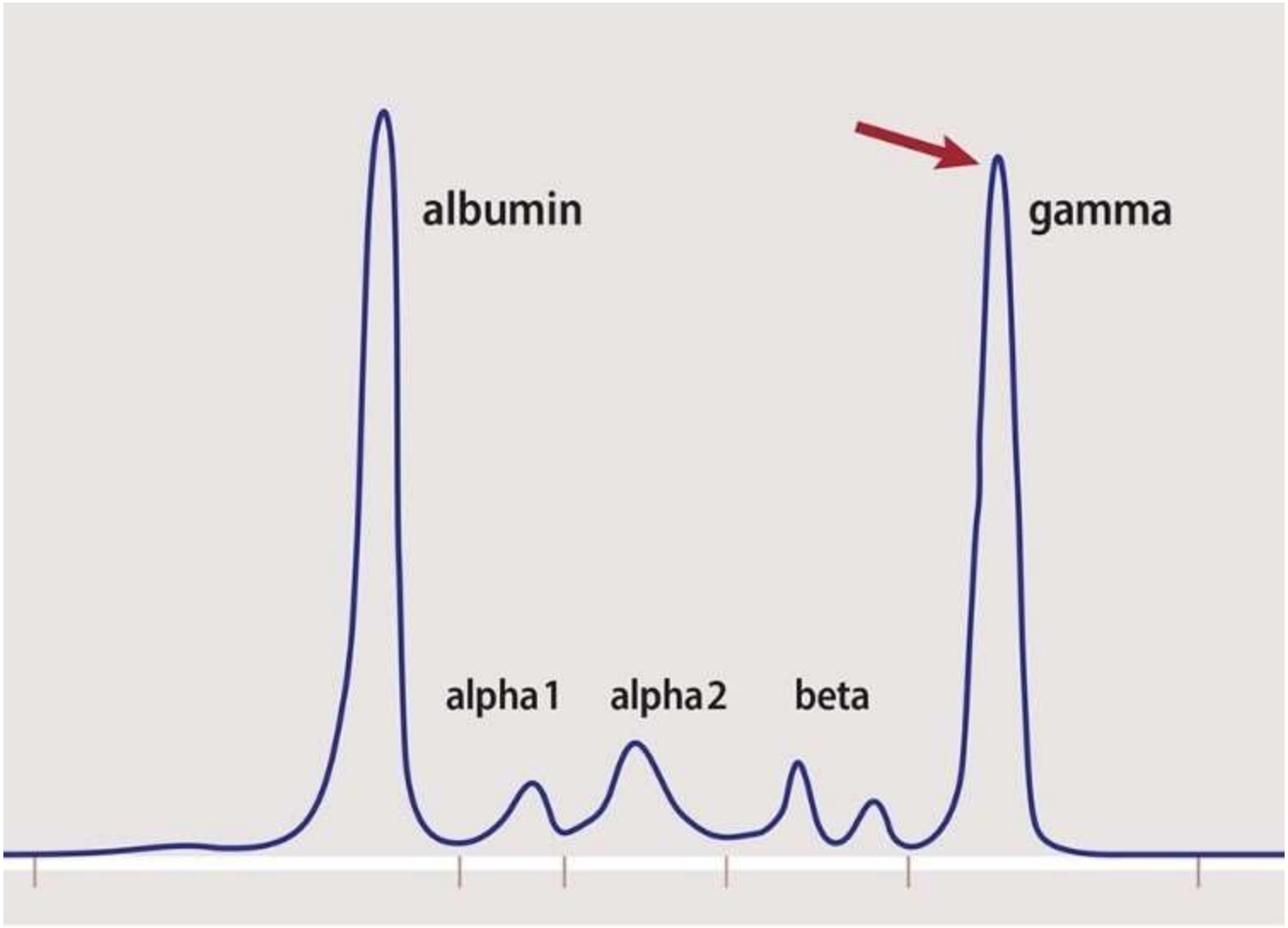
Abnormal result with myeloma cells producing the M-protein, creating an M-spike in the beta-2 zone

The result is your level of monoclonal protein (M-protein)



Serum protein electrophoresis (SPEP or SPE)

Serum protein electrophoresis (SPEP) is a test that measures the amount of heavy chain monoclonal protein made by myeloma cells→


albumin
gamma
alpha 1
alpha 2
beta

Diagnostic criteria for multiple myeloma

Major criteria[1]

- Marrow plasmacytosis >30%
- Plasmacytoma
- M-component
  - Serum IgG >3.5 g/dl or IgA >2 g/dl
- Urine Bence-Jones protein >1 g/24 h

Minor criteria[1]

- Marrow plasmacytosis of 10–30%
- M-component present
- Lytic bone lesions
- Immunoglobulin levels reduced to less than 50% of normal

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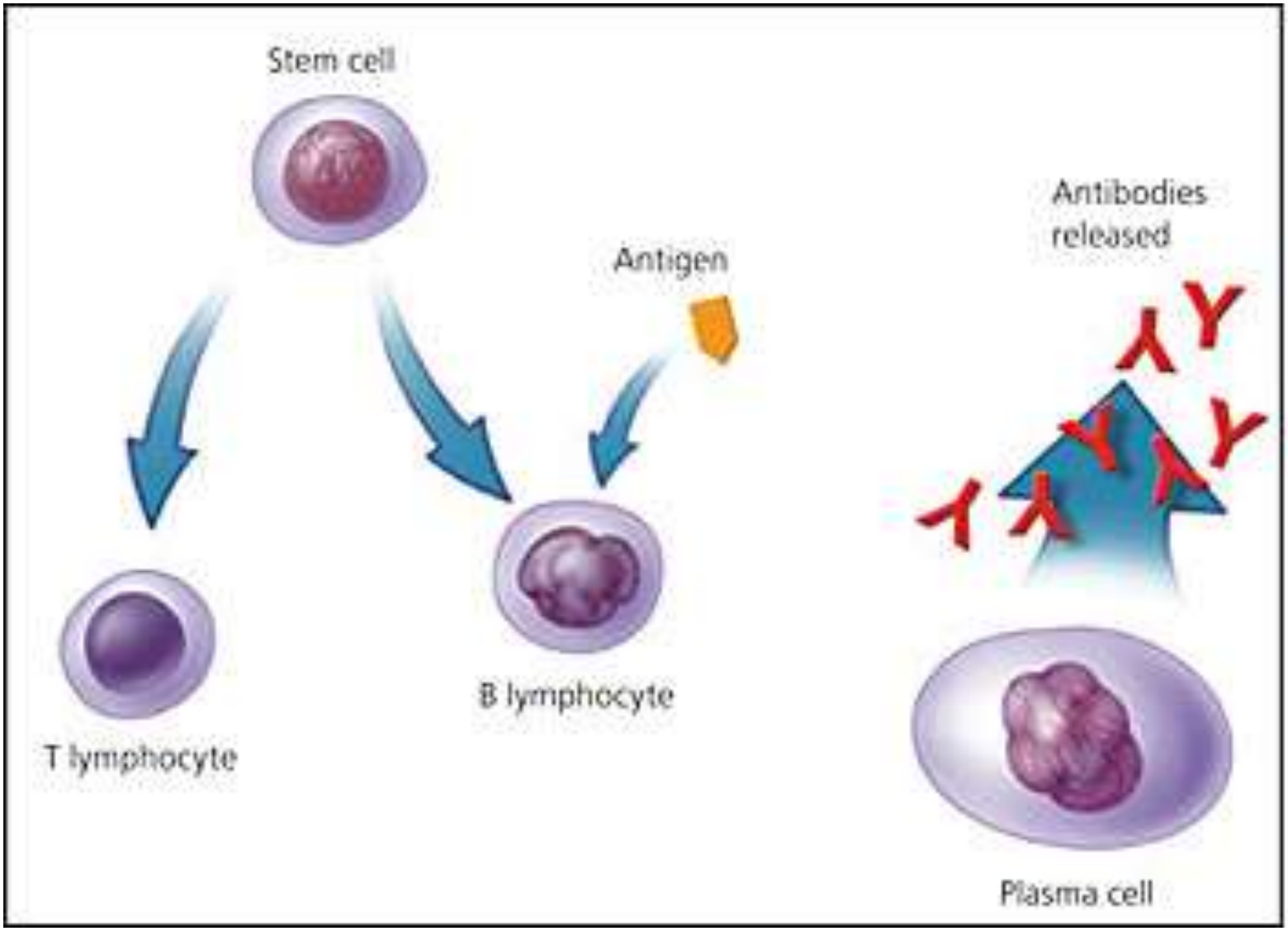
[1]The diagnosis of multiple myeloma requires one major and o

- Anamnesis and physical exam
- Complete blood count
- Creatinine and calcium value
- Serum protein electrophoresis, IgG, IgA, IgM dosage, and immunofixation
- Urine routine tests and 24-hr urine Bence-Jones protein
- Marrow aspirate and/or bone biopsy
- Cytogenetics (FISH)
- Skeleton X-ray (in selected circumstances magnetic resonance imaging)
- Serum Beta-2 microglobulin and LDH
- Free light-chain assay


Stem cell
Antigen
Antibodies released
T lymphocyte
B lymphocyte
Plasma cell
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Total proteins

High Albumin - rare but dehydration and shock.

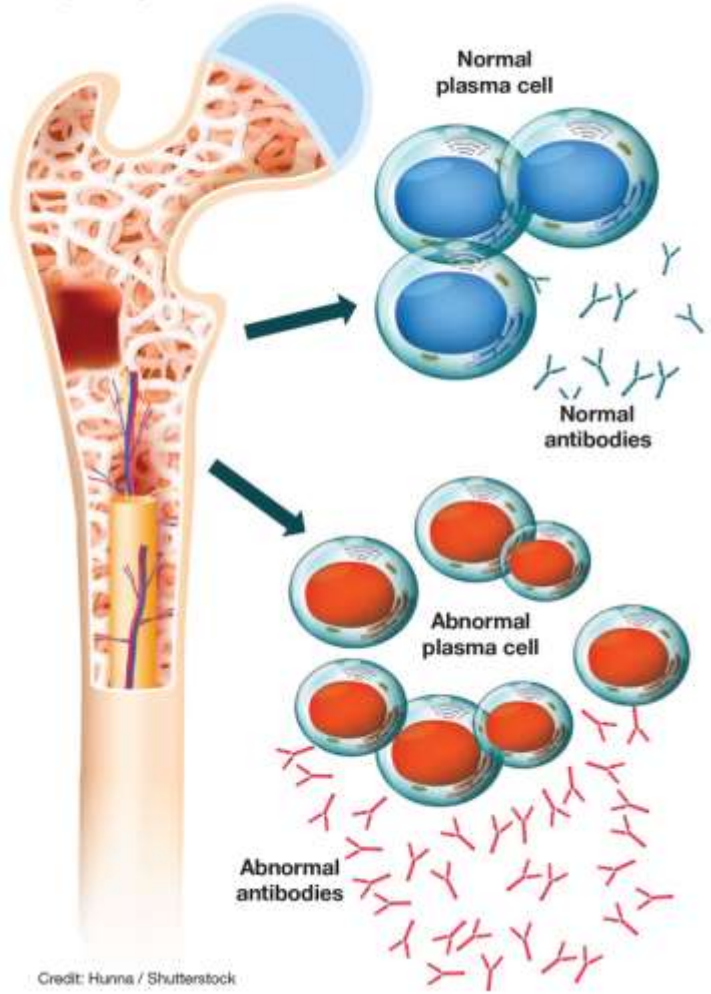
Low Albumin : same as proteins.

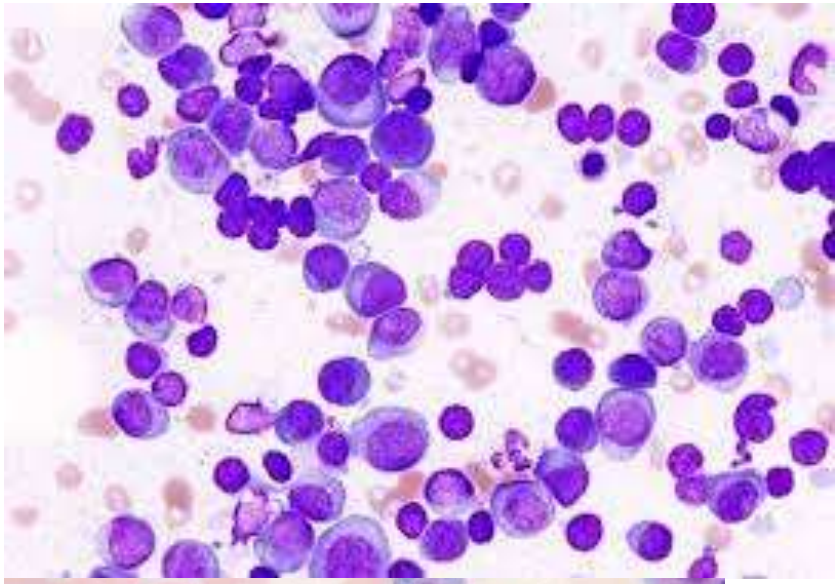
High Globulin : Multiple myeloma, Nephrosis, Chronic infections, Collagen diseases, Liver diseases

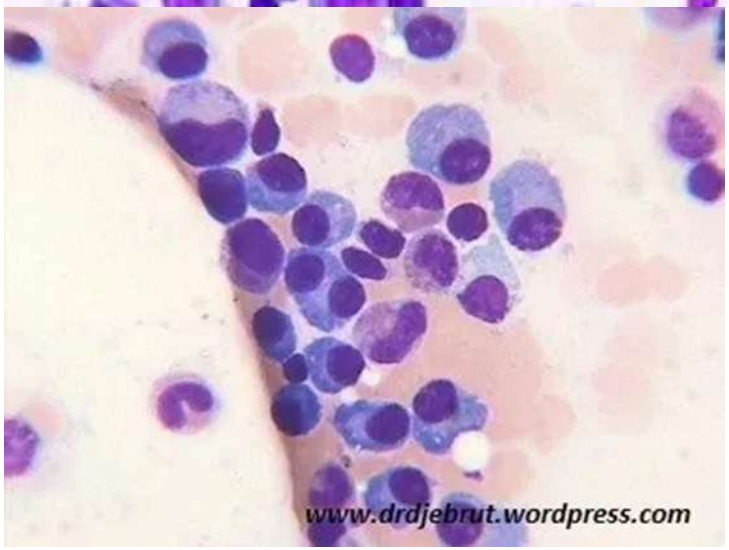
Low Globulin : Burns and severe malnutrition.

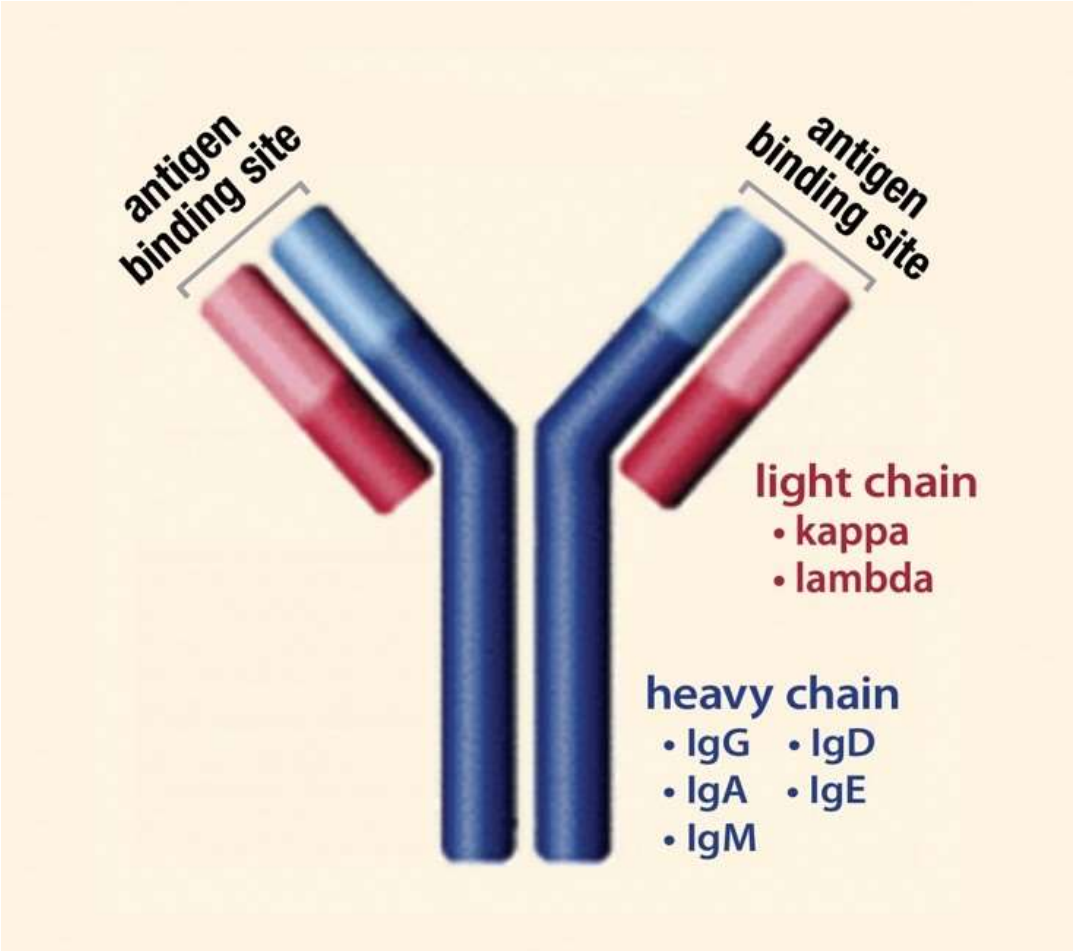
FIGURE 1

Multiple Myeloma in Bone Marrow

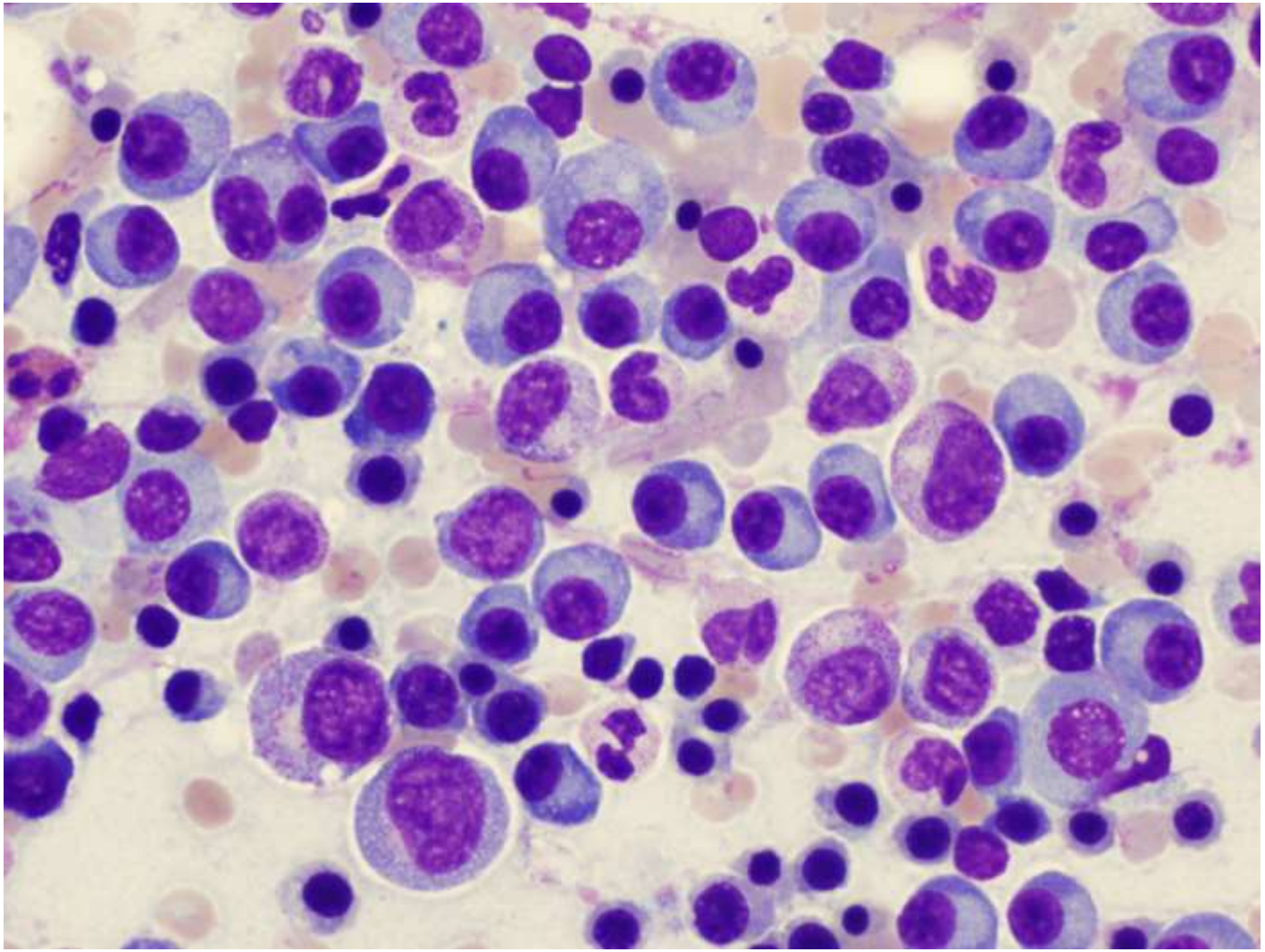








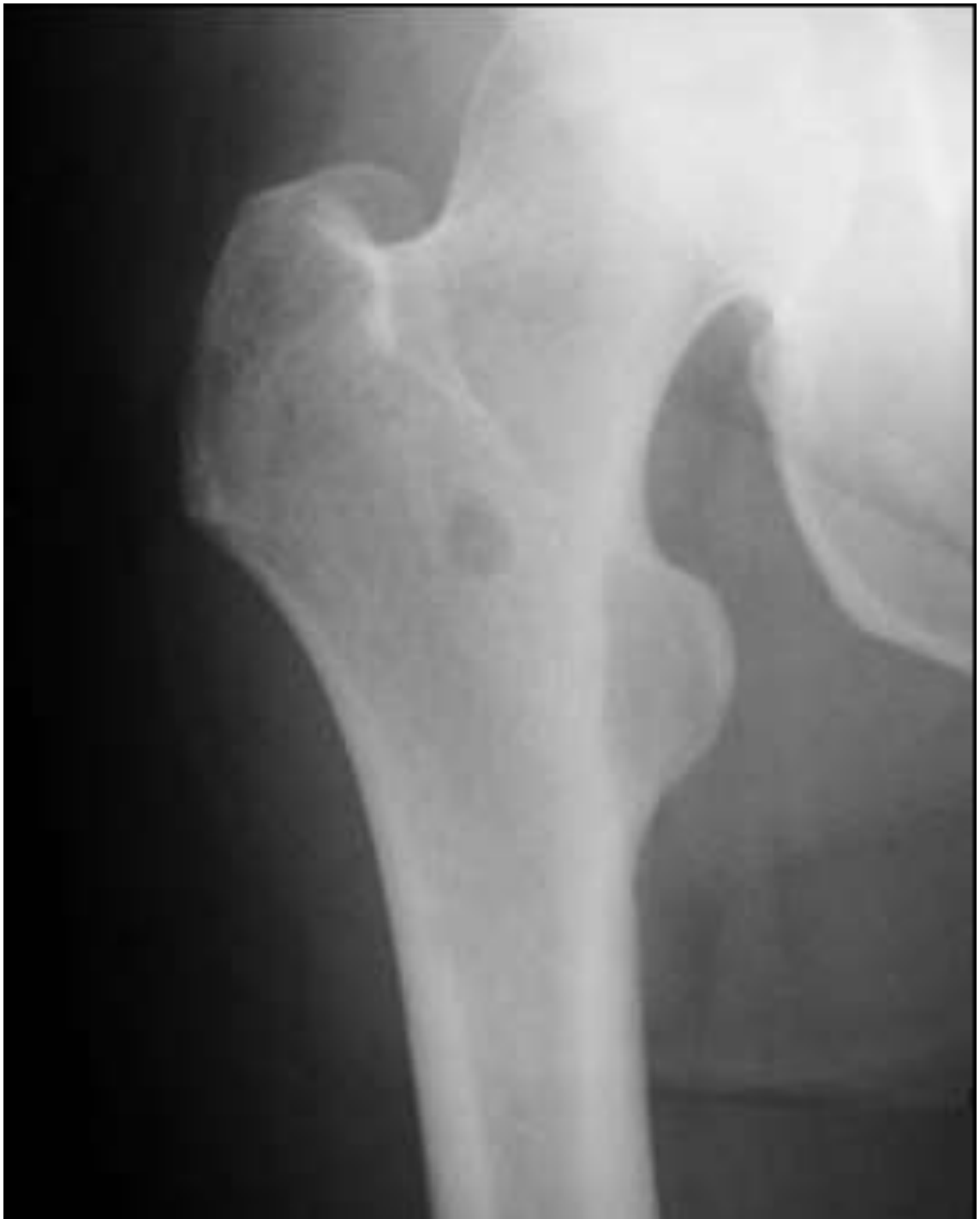
Immunoglobulin proteins are made up of two kinds of molecules, heavy chains and light chains



STAGING SYSTEMS FOR MULTIPLE MYELOMA

Stage	Durie-Salmon Criteria[1]	ISS Criteria[2]
I	All of the following: • Hemoglobin value >10 g/dL • Serum calcium value normal or ≤12 mg/dL • Bone x-ray, normal bone structure, or solitary bone plasmacytoma only • Low M-component production rate ‣ IgG value <5 g/dL; ‣ IgA value <3 g/dL ‣ Bence Jones protein <4 g/24 h	Serum beta-2 microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: • Hemoglobin value <8.5 g/dL • Serum calcium value >12 mg/dL • Advanced lytic bone lesions • High M-component production rate ‣ IgG value >7 g/dL; ‣ IgA value >5 g/dL ‣ Bence Jones protein >12 g/24 h	Serum beta-2 microglobulin ≥5.5 mg/L
Subclassification Criteria A Normal renal function (serum creatinine level <2.0 mg/dL) B Abnormal renal function (serum creatinine level ≥2.0 mg/dL)		

gambaran khas suatu lesi myeloma tunggal berupa gambaran lusen berbatas tegas pada regio interocanter. Lesi-lesi lebih kecil tampak pada trocanter



Plasma cells Disorders

- Multiple Myeloma (MM)
  - Neoplastic infiltration of bone and BM
  - M Immunoglobulin or light chains in the serum or urine
- Dx >30% plasma cells in BM
  - Serum M protein other than IgM
    - IgG >3g/dl
    - IgA >2g/dl
  - Urine M protein
    - 1g/24 hrs

Plasma cells Disorders

- 20% of patients lack the M protein in serum but show light chains protein in urine
- Diagnosis made in this cases by presence of hypogammaglobulinemia, lytic bone lesions, or plasmacytoma

Plasma cells Disorders

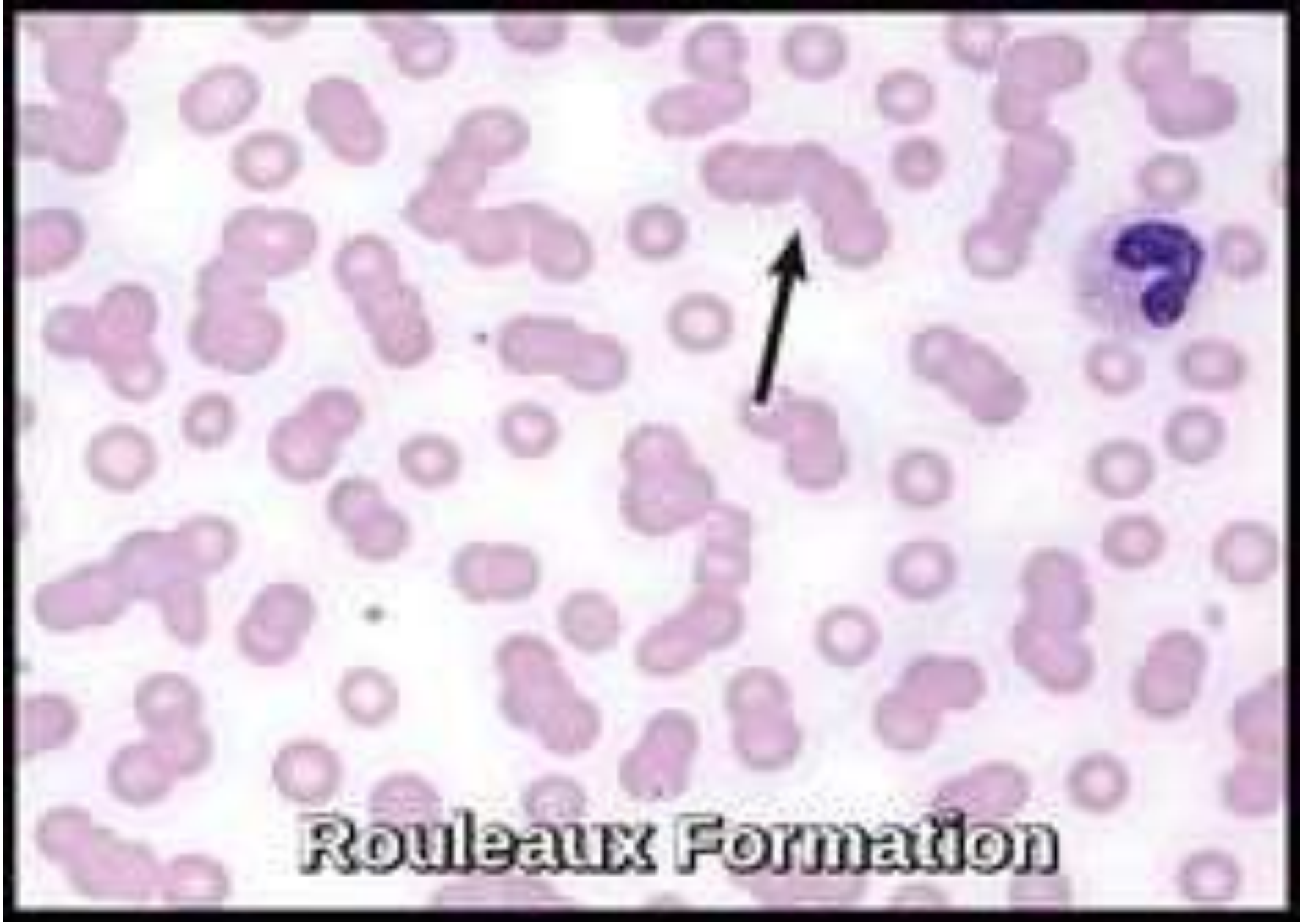
- Clinical Manifestations MM
- Results from
  - Bone or BM infiltration of Plasma Cells
  - Systemic effects of the M protein
  - And humoral immune deficiency

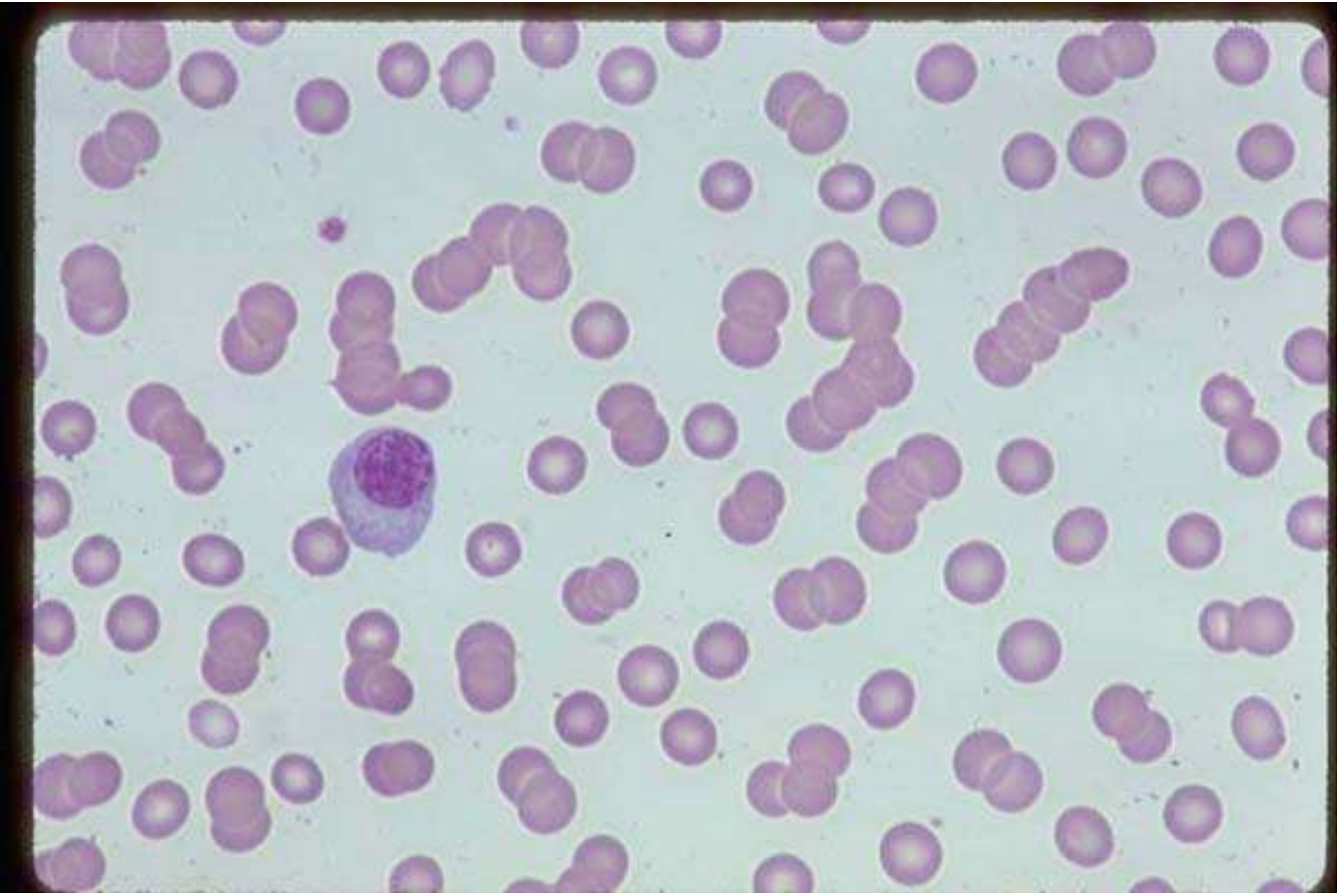
Plasma cells Disorders MM

- Bone Pain- Bone Xray-osteolytic -punched out lesions- low back and ribs
- Osteopenia-pathologic fractures-spinal cord compression
- Hypercalcemia - bony involvement
- Anemia - BM infiltration
- Decreased WBC and Plts less common
- Increased infections
- Renal insufficiency - hypercalcemia/uricemia

Plasma cells Disorders

- Lab Findings
- RBC morphology WNL - Rouleau formation
- Hallmark - paraprotein in SPEP
- Immunofixation to determine if monoclonal
- BM plasma cells 20-100% abnormal


Rouleaux Formation



Summary

- MDS is a heterogeneous group of clonal disorder bone marrow (stem cell neoplasm) marked by cytopenia and dysplasia of minimal one lineage.
- Diagnosis of MDS is mainly based on CBC, peripheral blood smear, bone marrow aspirate and biopsy→(depends on the presence of characteristic morfological change in the blood and marrow)
- Cytogenetic analysis and molecular biology is important to determine prognosis, and highly variable denpent on the subtype.
- Multiple myeloma is a clonal plasma cell proliferative disorder characterized by the abnormal increase of monoclonal immunoglobulins
- Laboratory tests (blood and urine)→Laboratory tests (blood)→Complete blood count (CBC)
- Serum Protein Electrophoresis (SPEP) assesses the amount of abnormal (monoclonal) protein, but does not identify its type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