Spot Diagnosis in Hematology and Counseling

Handout

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Outlines

Clinical Signs

CBC

Peripheal Blood Smear

Bone Marrow Aspiration

Hb typing

Coagulogram

Spot Diagnosis

โจทย์สั้นๆ ไม่พอที่จะวินิจฉัย เช่น

หญิง 35 ปี มาด้วยเรื่องซีดและมีเลือดออกตามไรฟัน

คำสั่ง

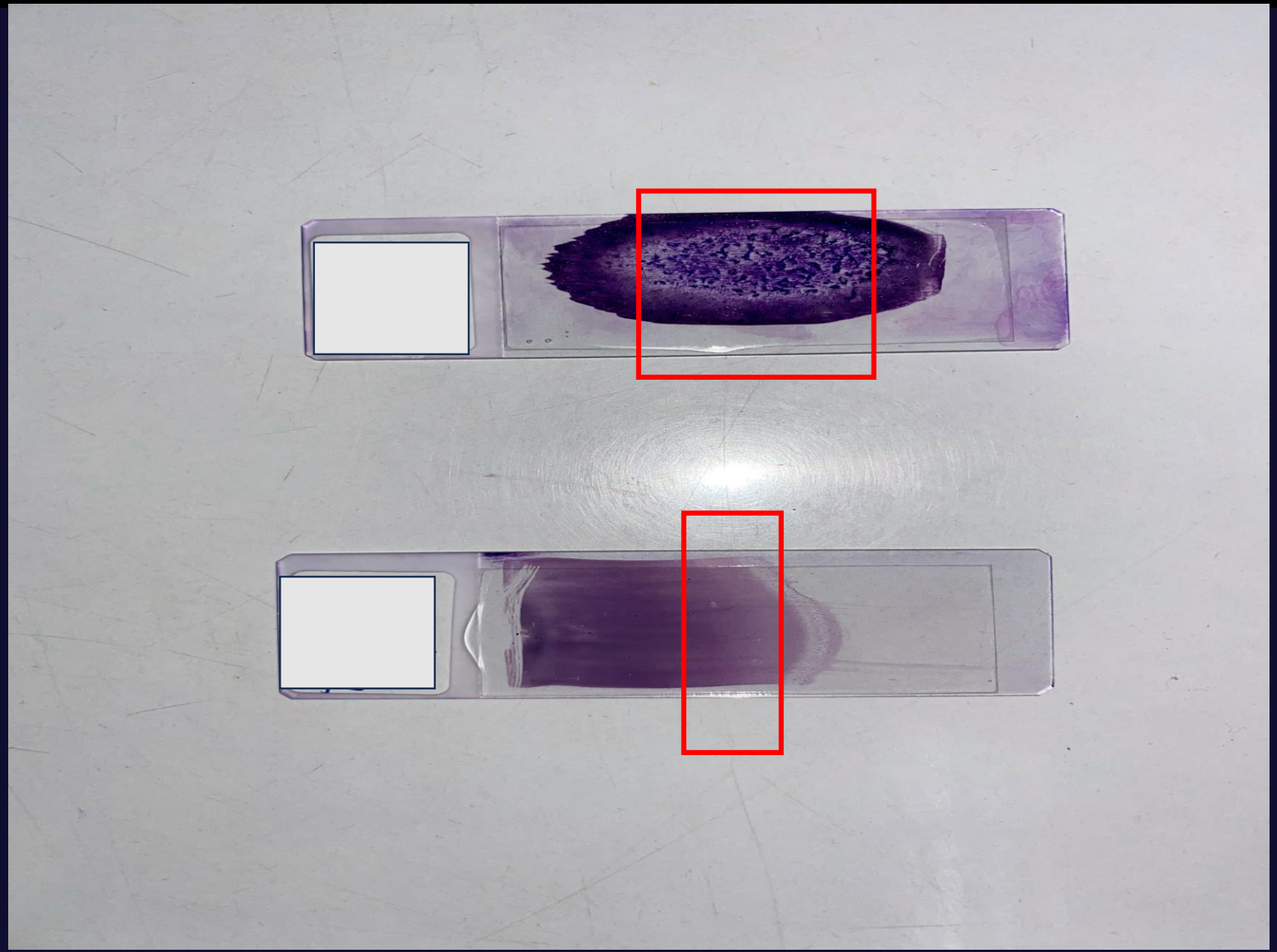
1.จงบรรยายเสมียร์เลือด

2.จงให้การวินิจฉัยโรคที่เป็นไปได้มากที่สุด

3.Investigation เพื่อยืนยันการวินิจฉัย

4.ให้การรักษาที่เหมาะสม

Spot Diagnosis



Case 1

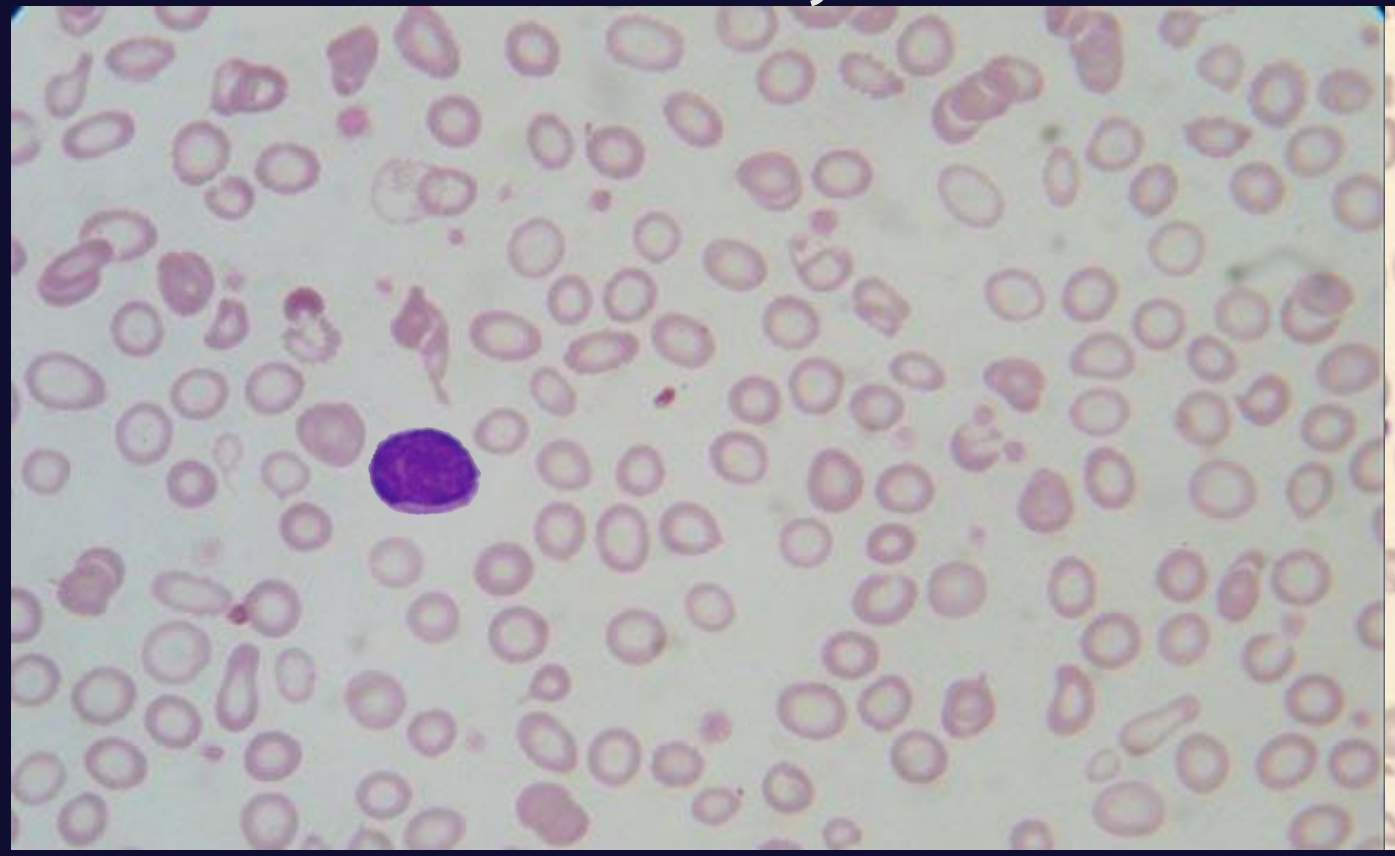
Male 78-year-old

chronic fatigue 3 months

PE: markedly pale

Blood Smear

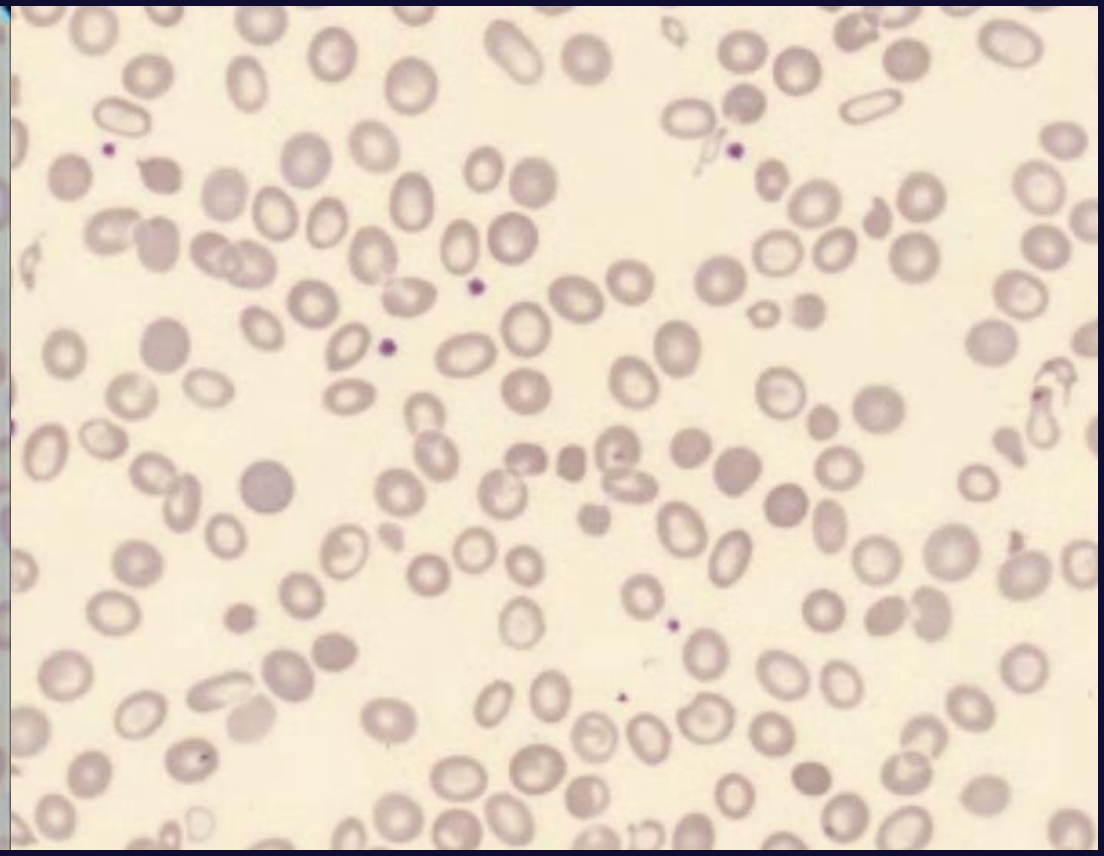
Iron Deficiency Anemia



HCMC, less anisopoikilocytosis

pencil cell, no hemolytic blood picture

Thalassemia

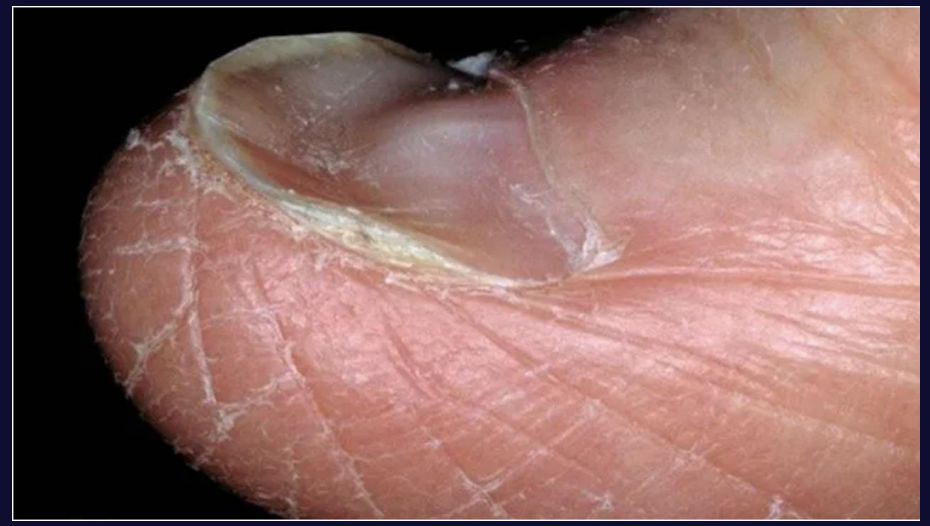


HCMC, anisopoikilocytosis

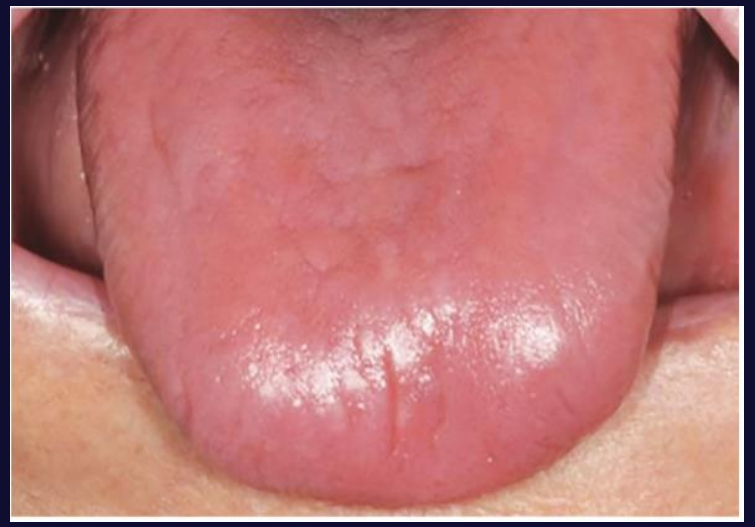
spherocyte, polychrome

Clinical Suggestion

Koilonychia



Glossitis



Iron Study

Interpretation of iron studies

	Iron deficiency	Chronic disease	Hemochromatosis	Pregnancy/ OCP use
Serum iron	↓	↓	↑	—
Transferrin or TIBC	↑	↓[a]	↓	↑
Ferritin	↓	↑	↑	—
% transferrin saturation (serum iron/TIBC)	↓↓	—/↓	↑↑	↓

↑↓ = 1° disturbance.

Transferrin—transports iron in blood.

TIBC—indirectly measures transferrin.

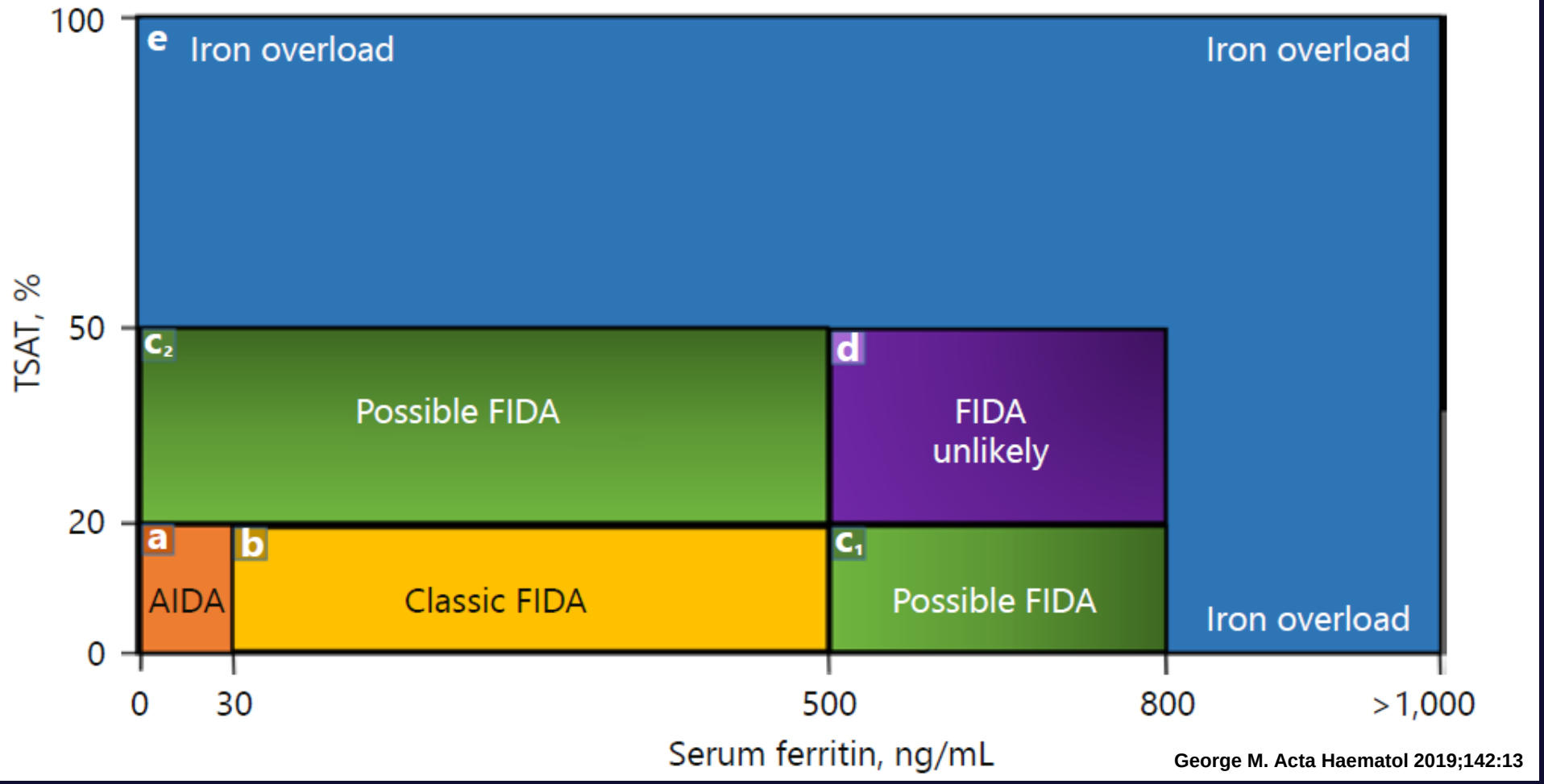
Ferritin—1° iron storage protein of body.

[a]Evolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

What if IDA + inflammation?

Ferritin จะสูง / Tsat จะต่ำ

Functional IDA



George M. Acta Haematol 2019;142:13

Chronic inflame

CKD

Role of iron

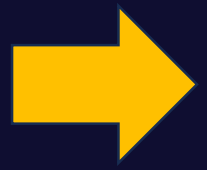
- prefer IV

Management

Iron supplement

Oral:

- Ferrous fumarate
- Ferrous gluconate
- Ferrous sulphate



Advice

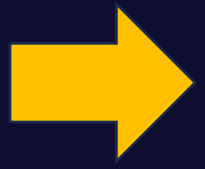
Duration atleast 3-6 mo.

Side effect: N/V, constipation

หลีกเลี่ยงกินพร้อมยาลดกรด แคลเซียม

Intravenous:

- Iron sucrose
- Ferric carboxymaltose



Side effect: allergy

Follow then repeat ~3-6 mo.

Management

หาสาเหตุของการขาดธาตุเหล็ก

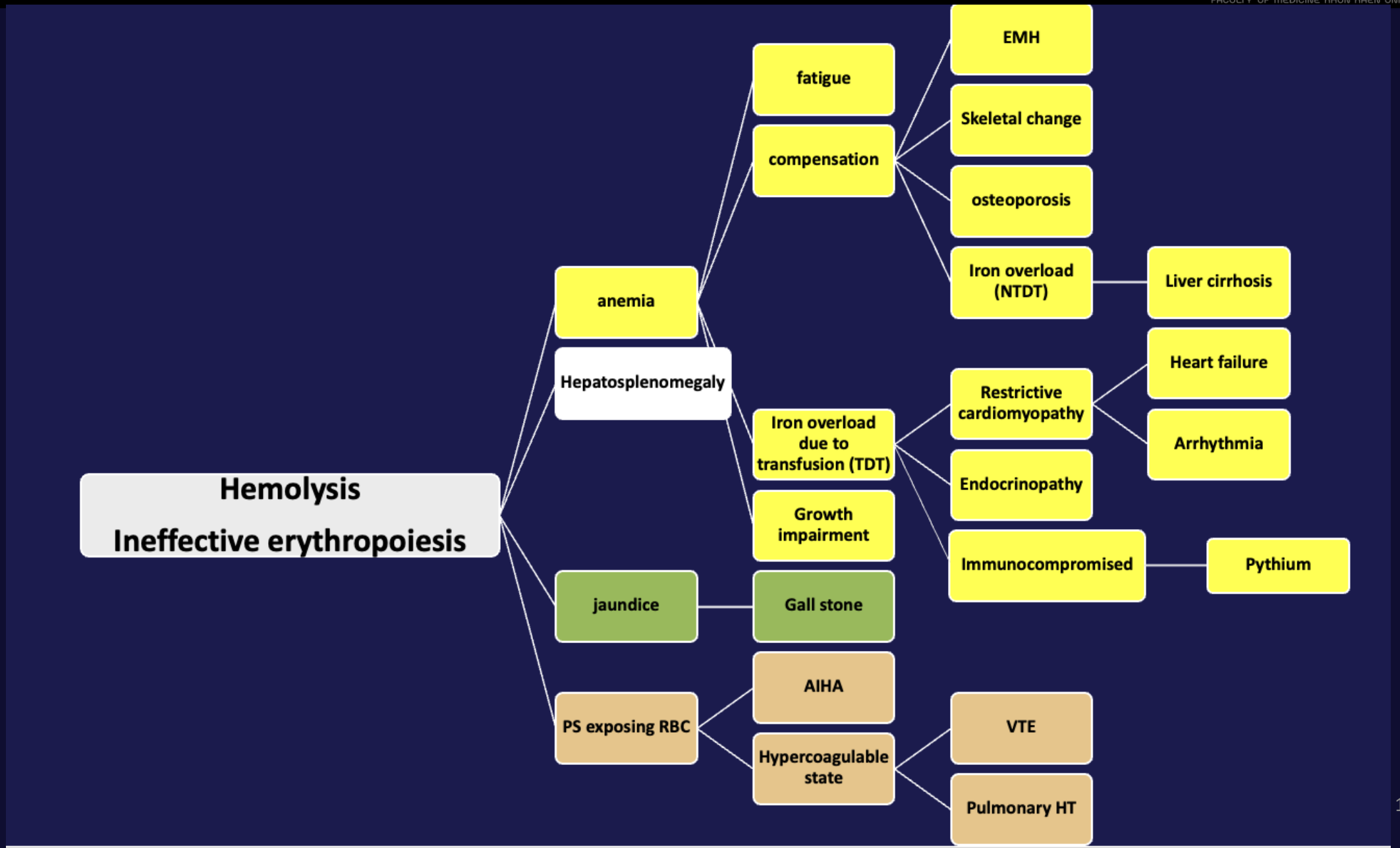
Occult GI blood loss

- NSAID
- GI malignancy

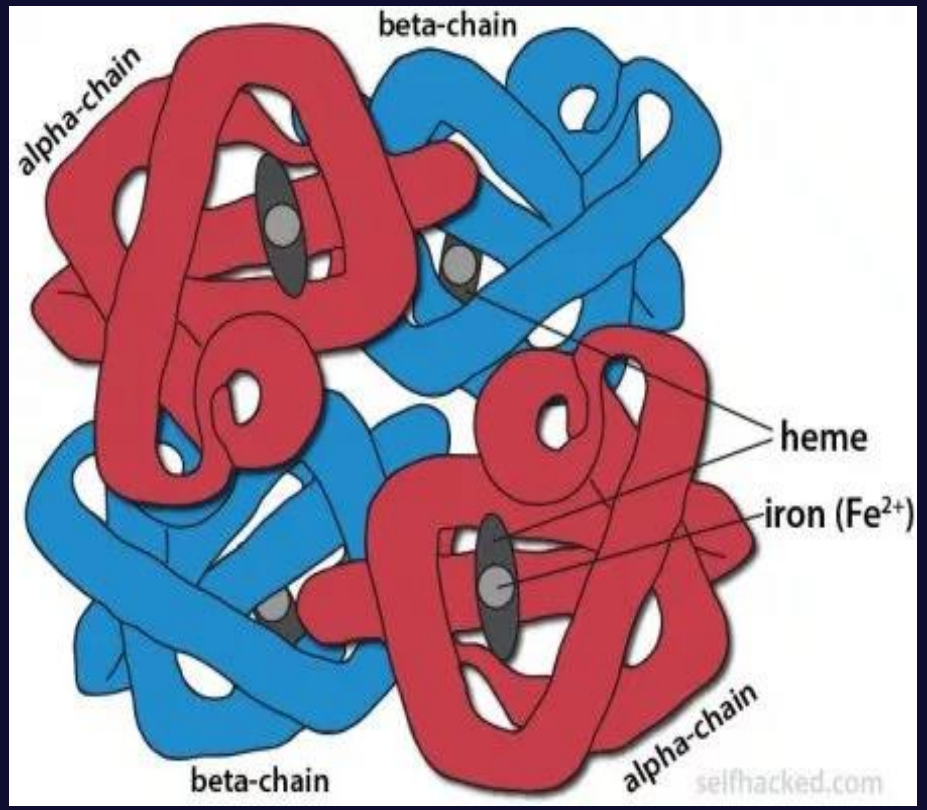
Hypermenorrhea

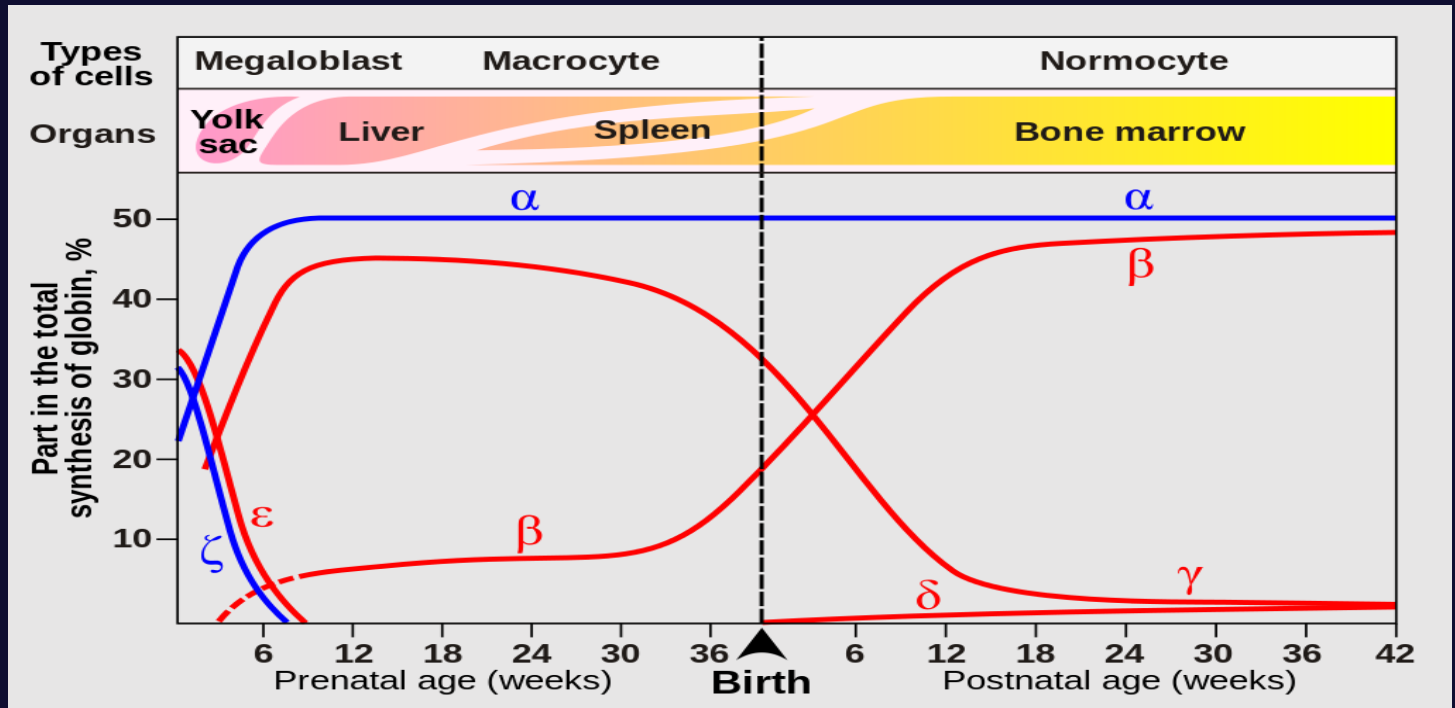
Chronic intravascular hemolysis

Clinical of Thalassemia



Hemoglobin Typing





Type of hemoglobin	Structure	Age at which they are present
Adult hemoglobin (HbA)	$\alpha_2\beta_2$	Adults
Hemoglobin A_2	$\alpha_2\delta_2$	Very small amount (3%) in adults.
Fetal hemoglobin (HbF)	$\alpha_2\gamma_2$	Fetal life
Hb Portland	$\zeta_2\gamma_2$	Embryonic life
Gower - 1	$\zeta_2\varepsilon_2$	Embryonic life
Gower – 2	$\alpha_2\varepsilon_2$	Embryonic life
Hemoglobin Barts	γ_4	Fetal life. Increases in thalassemia

Hemoglobin Typing

- A2A = α, **β**, δ, γ
  normal (aa/aa)
- A2ABartH = α, **β**, δ, γ
- CSA2A = α, **β**, δ, γ, CS
- CSA2ABartH = α, **β**, δ, γ, CS

- A2F = α, δ, γ
- A2FA = α, **β**, δ, γ
- EA = α, **β**, δ, γ, β^E
- EE = α, δ, γ, β^E
- EFA = α, **β**, δ, γ, β^E
- EF = α, δ, γ, β^E

Hemoglobin Typing

- EABart = **α, β, β^E, δ, γ**

- EFBart = **α, β^E, δ, γ**

- EFABart = **α, β, β^E, δ, γ**

- CSEABart = **α, β, β^E, δ, γ**, CS

- CSEFBart = **α, β^E, δ, γ**, CS

- CSEFABart = **α, β, β^E, δ, γ**, CS

Hemoglobin Typing

- Hb typing ที่ r/o alpha thal1 trait ได้ คือ
  - EA E 25-35%
  - A2A A2<3.5% และ screening test neg ก็คือเราๆคนปกติ
- Alpha thal1 trait (_ _/ α α) กับ homozygous alpha thal2 (_ α/_ α) แยกจากกันไม่ได้ด้วย typing
- ไม่มี typing ใด rule out alpha thal2 trait ได้ แม้แต่เราๆ

Case 2

A 73-year-old man, no underlying disease

Anemia with anemic symptoms 3 wks

Neither lymphadenopathy nor hepatosplenomegaly

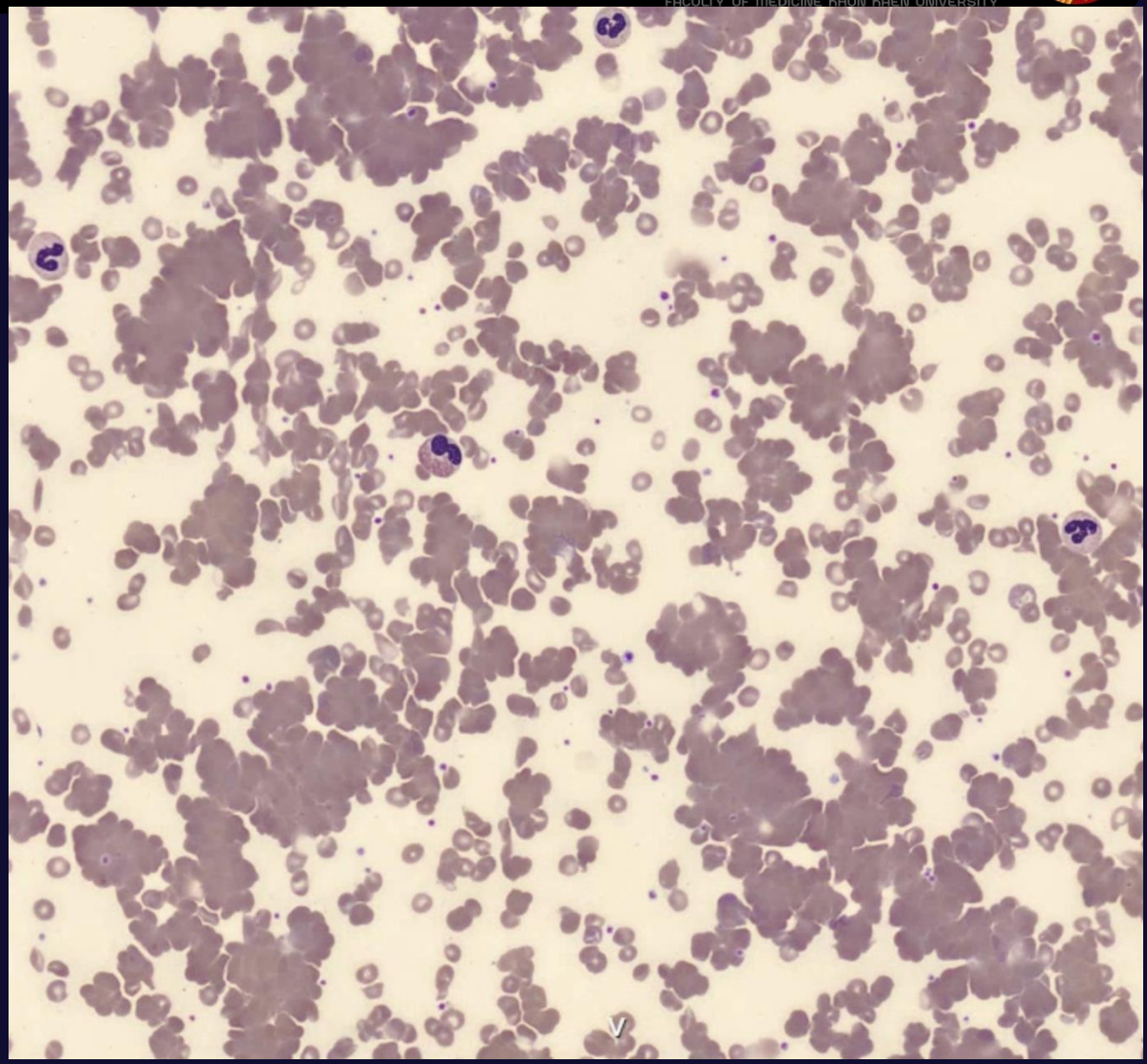
CBC and PBS

CBC / EDTA blood

RBC	2.82	10^6/uL	L	4.70 - 6.20
HGB ตรวจสอบซ้ำแล้ว	6.0	g/dL	LL	13.0 - 16.7
HCT	18.5	%	L	40.5 - 50.8
MCV	85.9	fL	L	80.0 - 97.8
MCH	21.3	pg	L	25.2 - 32.0
MCHC	32.4	g/dL	-	29.9 - 34.3
RDW	27.5	%	H	11.9 - 14.8
WBC	5.97	10^3/uL	-	4.60 - 10.60
PLT	272	10^3/uL	-	173 - 383
MPV	—	fL	-	8.7 - 12.5
Plt smear	Adequate		-	
NE%	77.2	%	H	43.7 - 70.9
LY%	15.3	%	L	20.1 - 44.5
MO%	5.8	%	-	3.4 - 9.8
EO%	1.3	%	-	0.7 - 9.2
BA%	0.4	%	-	0.0-2.6

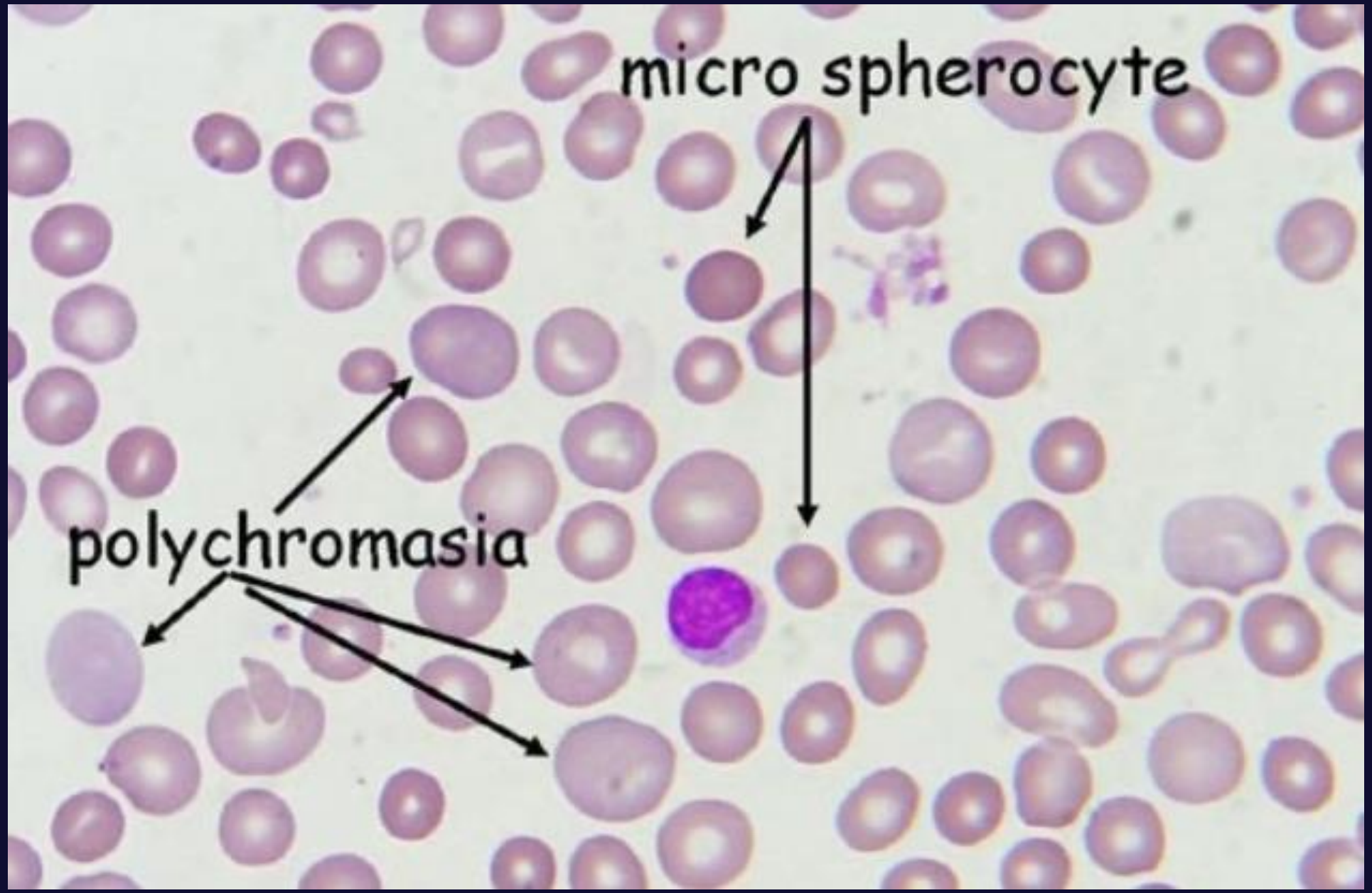
CBC Remark

RBC agglutination were seen, Sample was incubated 37c before analysis.



Autoagglutination

Extravascular Hemolysis



Hemolysis Laboratory

- Hemolytic marker (IVH and EVH)
  - LDH
  - Indirect hyperbilirubinemia
  - Reticulocytosis (ARC>100,000)
- Intravascular
  - Low serum haptoglobin
  - Urine blood positive without RBC
  - Schistocyte or bite cell/ghost cell in PBS
- Extravascular
  - Microspherocyte

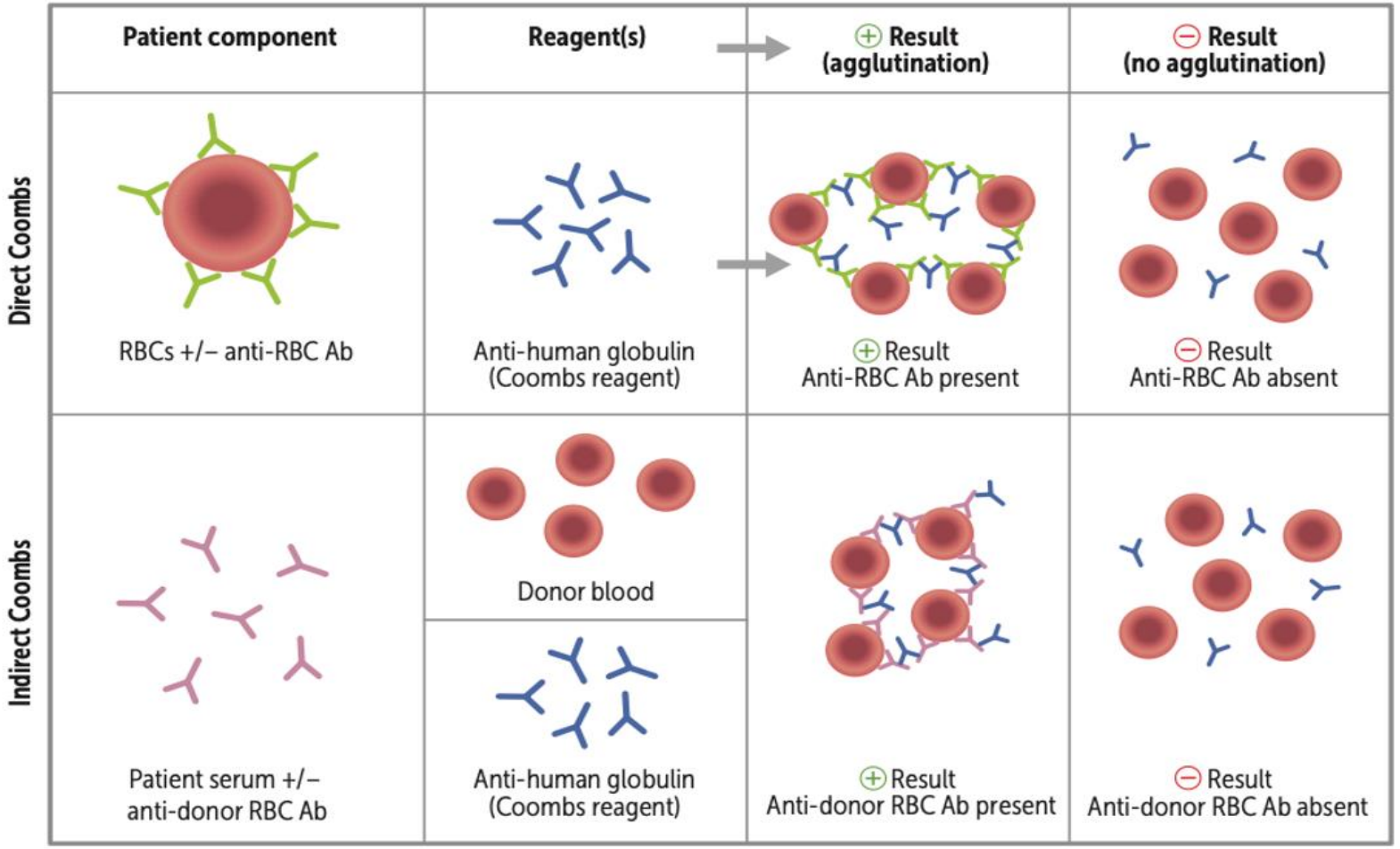
Direct Antiglobulin Test

Coombs test

Also called antiglobulin test. Detects the presence of antibodies against circulating RBCs.

Direct Coombs test—anti-Ig antibody (Coombs reagent) added to patient's RBCs. RBCs agglutinate if RBCs are coated with Ig. Used for AIHA diagnosis.

Indirect Coombs test—normal RBCs added to patient's serum. If serum has anti-RBC surface Ig, RBCs agglutinate when Coombs reagent is added. Used for pretransfusion testing.



About Cold Agglutinin Disease

IgM mediated:

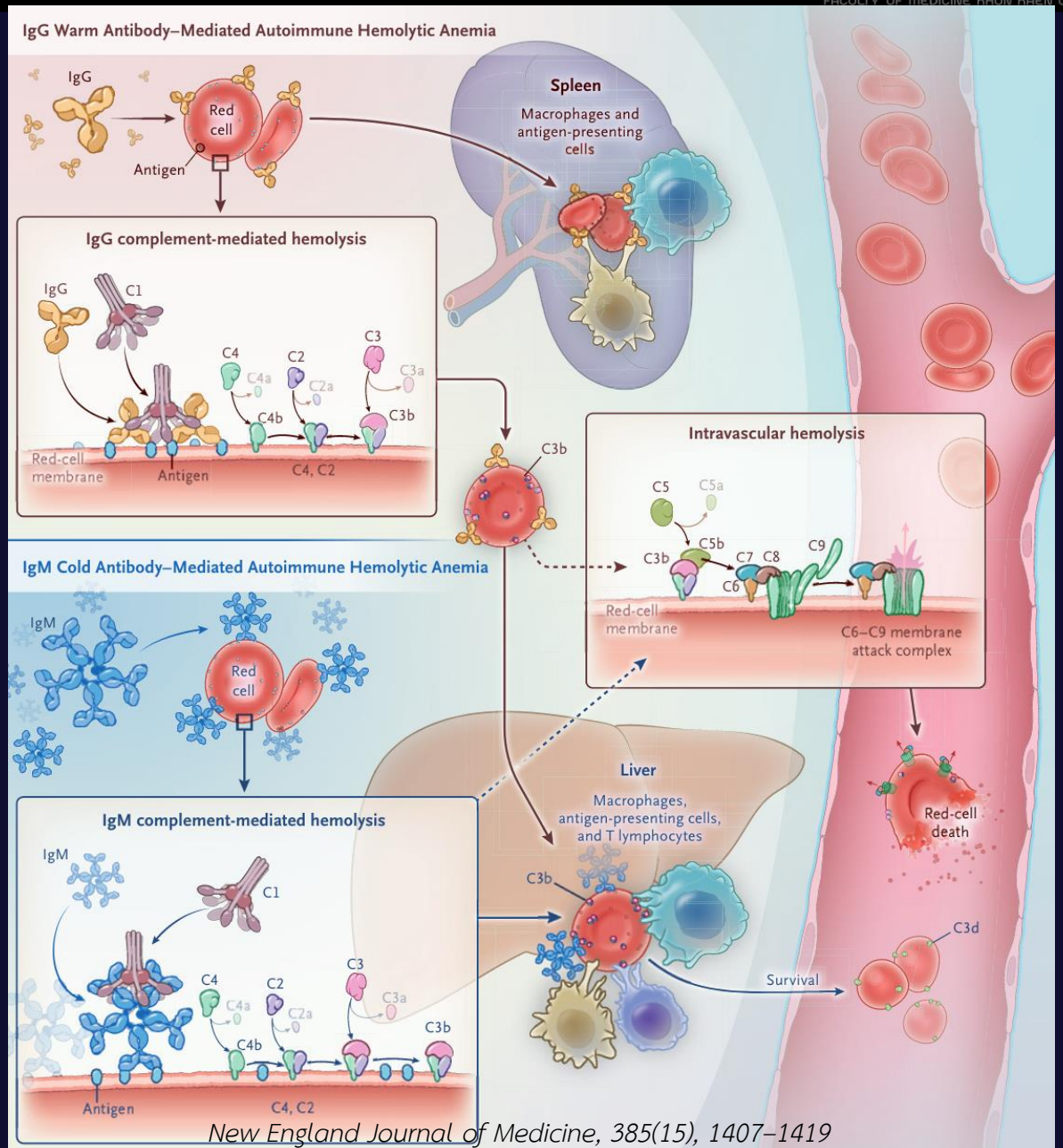
Best activated at 4°C

Extravascular Hemolysis

- Liver > Spleen

Some of intravascular

Less spherocyte in PBS



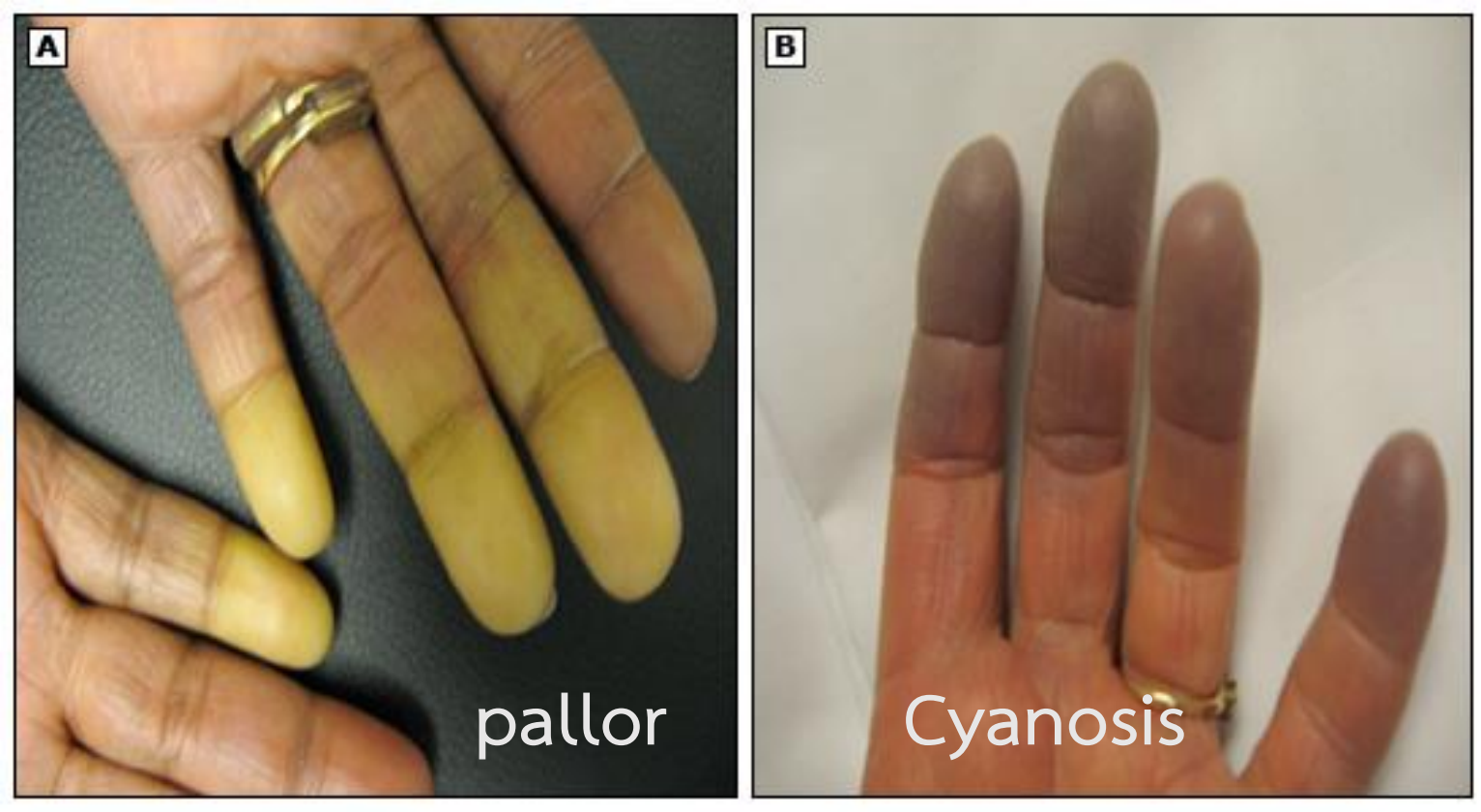
New England Journal of Medicine, 385(15), 1407–1419

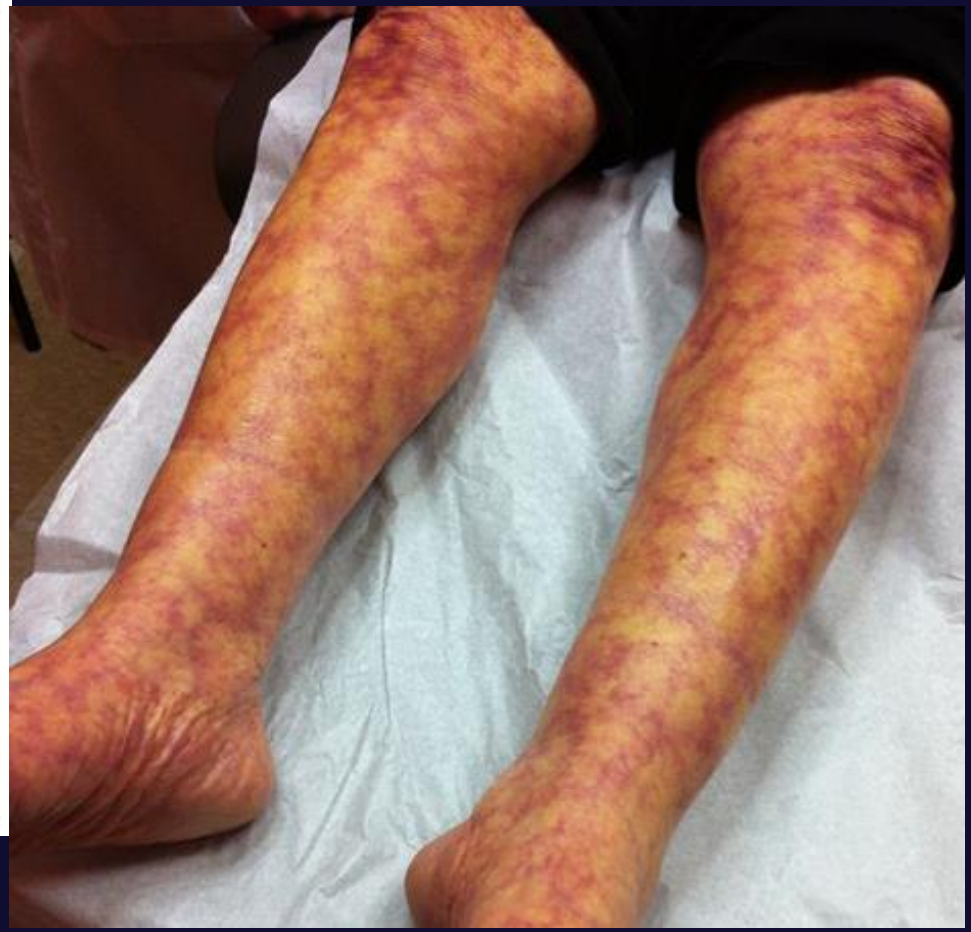
1.Haematologica. 2006;91(4):460.

Cold-induced Symptoms

Cold agglutinin → RBC agglutination → Impaired blood flow

Raynaud phenomenon: Little or no reactive hyperemia





Found ~50%

uptodate.com

Diagnostic Clues

Serum cold agglutinin titer ≥ 1:64 (4°C 1-2 hrs)

Cold-Induced Symptoms

Hemolysis: LDH, Haptoglobin, Bilirubin , Reticulocytosis

Agglutination: High MCV, Low Hct than Hb, PBS

DAT: +++C3d, -/+IgG(~20%)[1]

1.*Haematologica, 91 4*, 460-6

2.Infusionsther Transfusionsmed. 1994;21(6):410

Raynaud Phenomenon

Primary

Secondary

- Autoimmune: SLE, Scleroderma, DM, RA
- Cryoglobulinemia, Cryofibrinogenemia
- Environment: Vibration, Cold
- Chemical: Vinyl Chloride
- Medication: Platinum CMT

Treatment of AIHA

- Treat precipitate casuse
- Severe anemia
  - Least incompatible / Most compatible red cell
- Immunosuppression

1st line:

Corticosteroid: Prednisolone / Dexamethasone [Warm type]

Rituximab [Cold type]

Anti-complement: Sutimlimab [Cold type]

2nd line:

Rituximab

Splenectomy (not for cold type)

Cyclophosphamide

Cyclosporin

Bendamustine

Haematologica. 2006;91(4):460

Adjunctive Treatment for Cold Type

- Cold avoidance
- Warmed red cell transfusion
- Erythroid stimulating agents high dose (10,000-80,000 IU/wk)[1]
- Plasmapheresis: 1-1.5x replace with albumin for emergency[2]
- [3]Thromboprophylaxis in high risk patient
  - untreated with severe anemia / exarcerbation

1.*Transfusion Medicine and Hemotherapy*, *41*(6), 462–468

2.*Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis*

3.*New England Journal of Medicine*, *385*(15), 1407–1419

Other Cold-Related Hematologic Disorder

Paroxysmal cold hemoglobinuria

- Polyclonal IgG to P antigen
- Biphasic antibody (Donath-Landsteiner antibody)
  - Antibody binds and fix complement in cold temperature
  - Intravascular hemolysis in warm temperature

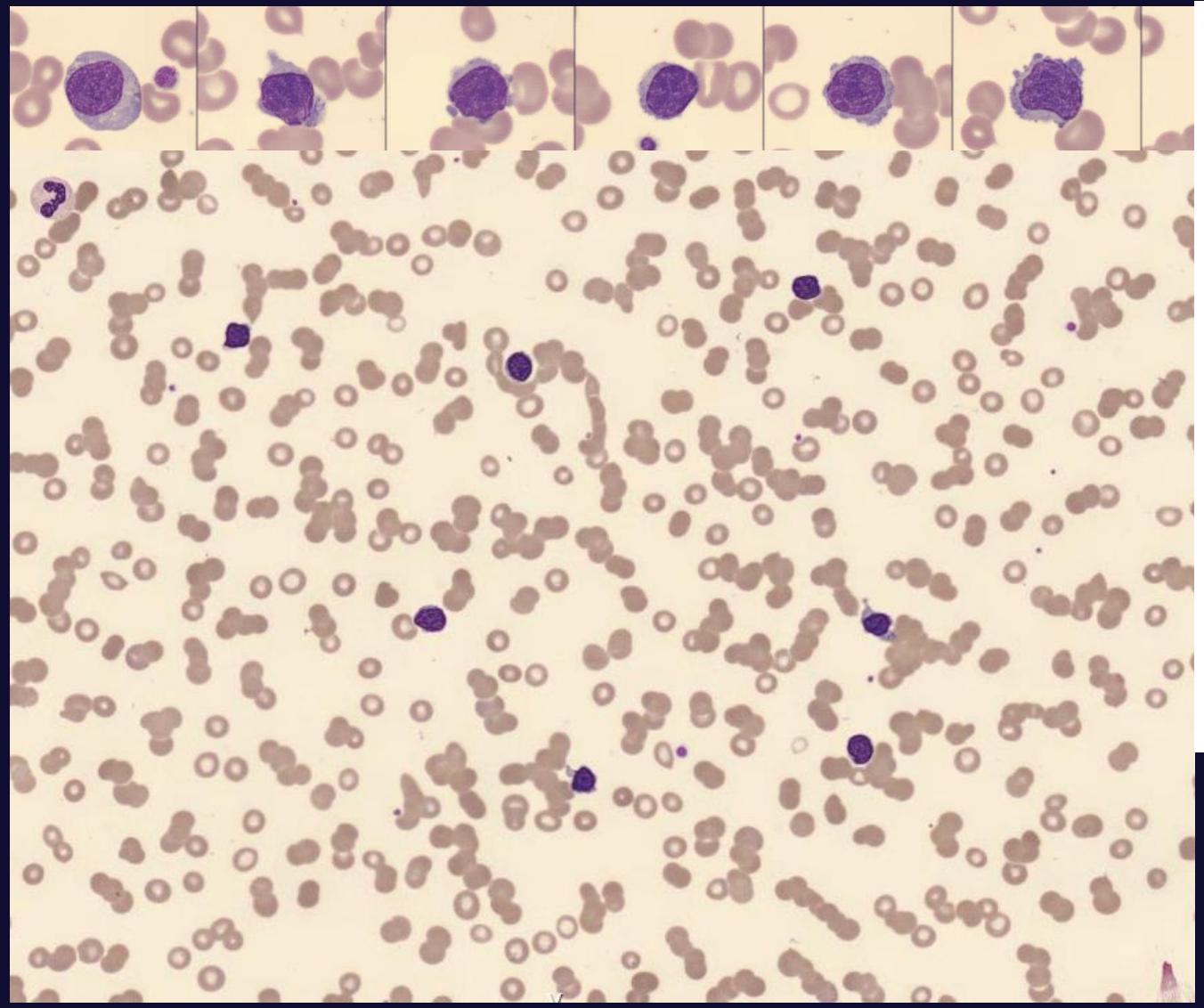
Cryoglobulinemia: serum

Cryofibrinoginemia: plasma

- No hemolysis

New England Journal of Medicine, *385*(15), 1407–1419

Lymphoma with Evans Syndrome

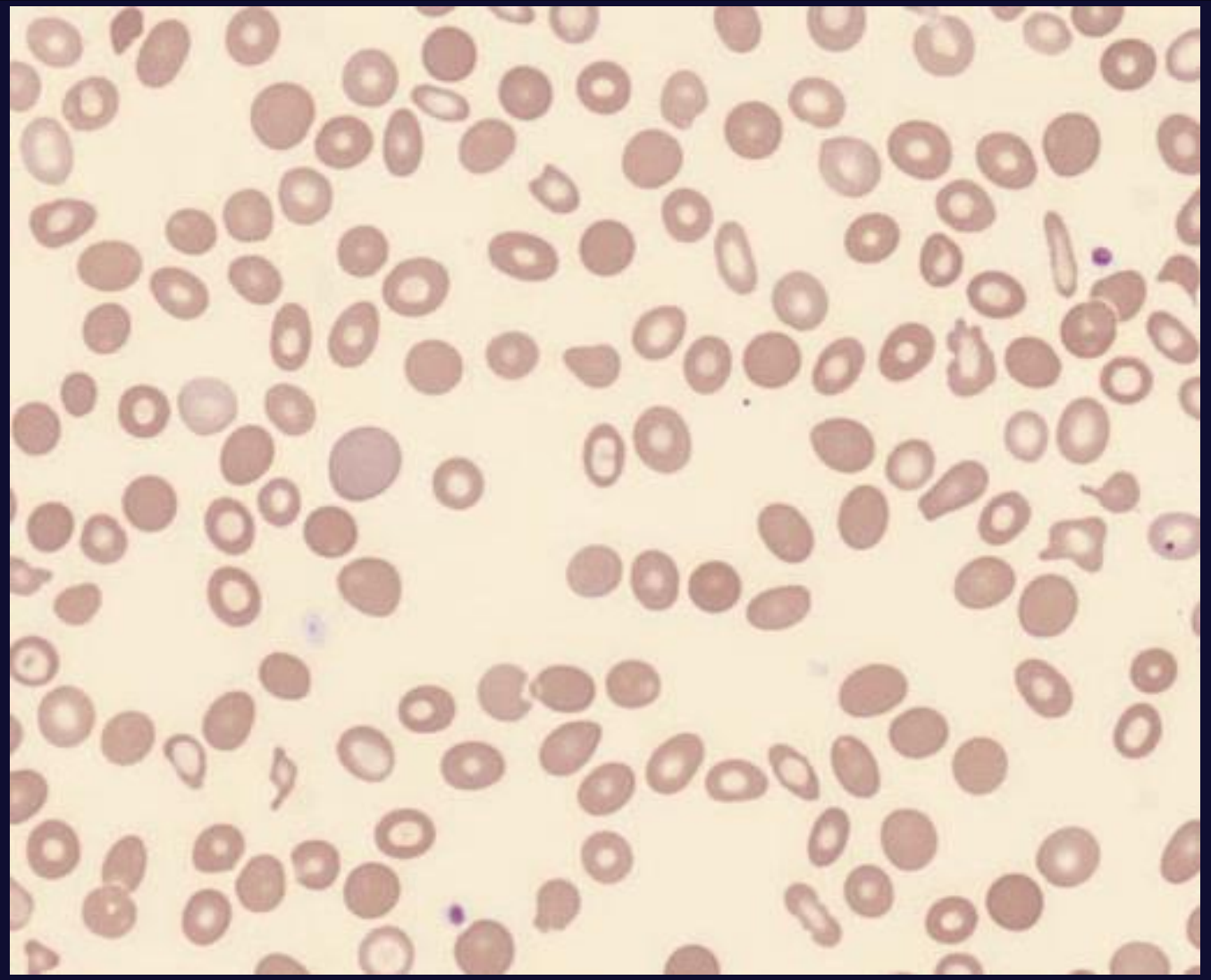


CBC / EDTA blood				
RBC	1.23	10^6/uL	L	4.70 - 6.20
HGB ตรวจสอบซ้ำแล้ว	4.0	g/dL	LL	13.0 - 16.7
HCT	14.6	%	L	40.5 - 50.8
MCV	118.7	fL	H	80.0 - 97.8
MCH	32.5	pg	H	25.2 - 32.0
MCHC	27.4	g/dL	L	29.9 - 34.3
RDW	20.1	%	H	11.9 - 14.8
WBC	25.19	10^3/uL	H	4.60 - 10.60
PLT	32	10^3/uL	L	173 - 383
MPV	11.4	fL	-	8.7 - 12.5
Plt smear	Decreased		-	
NE%	3.0	%	L	43.7 - 70.9
LY%	85.0	%	H	20.1 - 44.5
MO%	3.0	%	L	3.4 - 9.8
EO%	0.0	%	L	0.7 - 9.2

DAT pos 3+

Glo = 6.2 g/dL

PNH with IDA



Retic / EDTA blood		
RETICULOCYTE COUNT	3.07	%
Reticulocyte hemoglobin equivalent (Ret-He)	18.70	pg
CBC / EDTA blood		
Hb	8.3	g/dL
RBC	3.80	10^6/uL
HCT	28.7	%
MCV	75.5	fL
MCH	21.8	pg
MCHC	28.9	g/dL
RDW	21.6	%
WBC	5.49	10^3/uL
PLT	88	10^3/uL
Serum Iron / Clot blood	26	ug/dl
TIBC / Clot blood	360	ug/dL
Transferin saturated(%) / Clot blood	7.2	%
Ferritin / Clot blood	17	ng/ml

LDH 980 IU/ml

Absent of CD55/59 from blood for flow cytometry

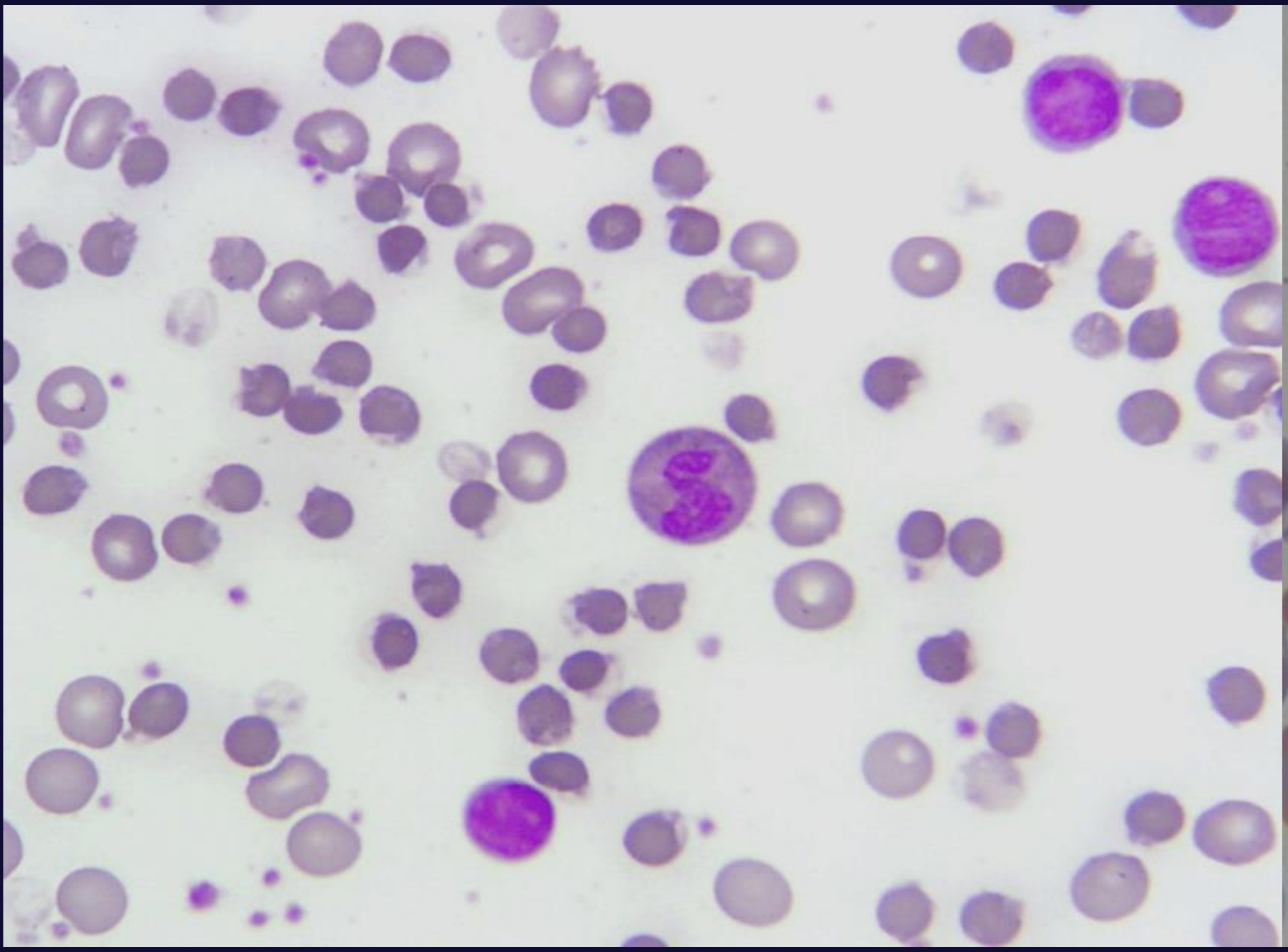
Case 3

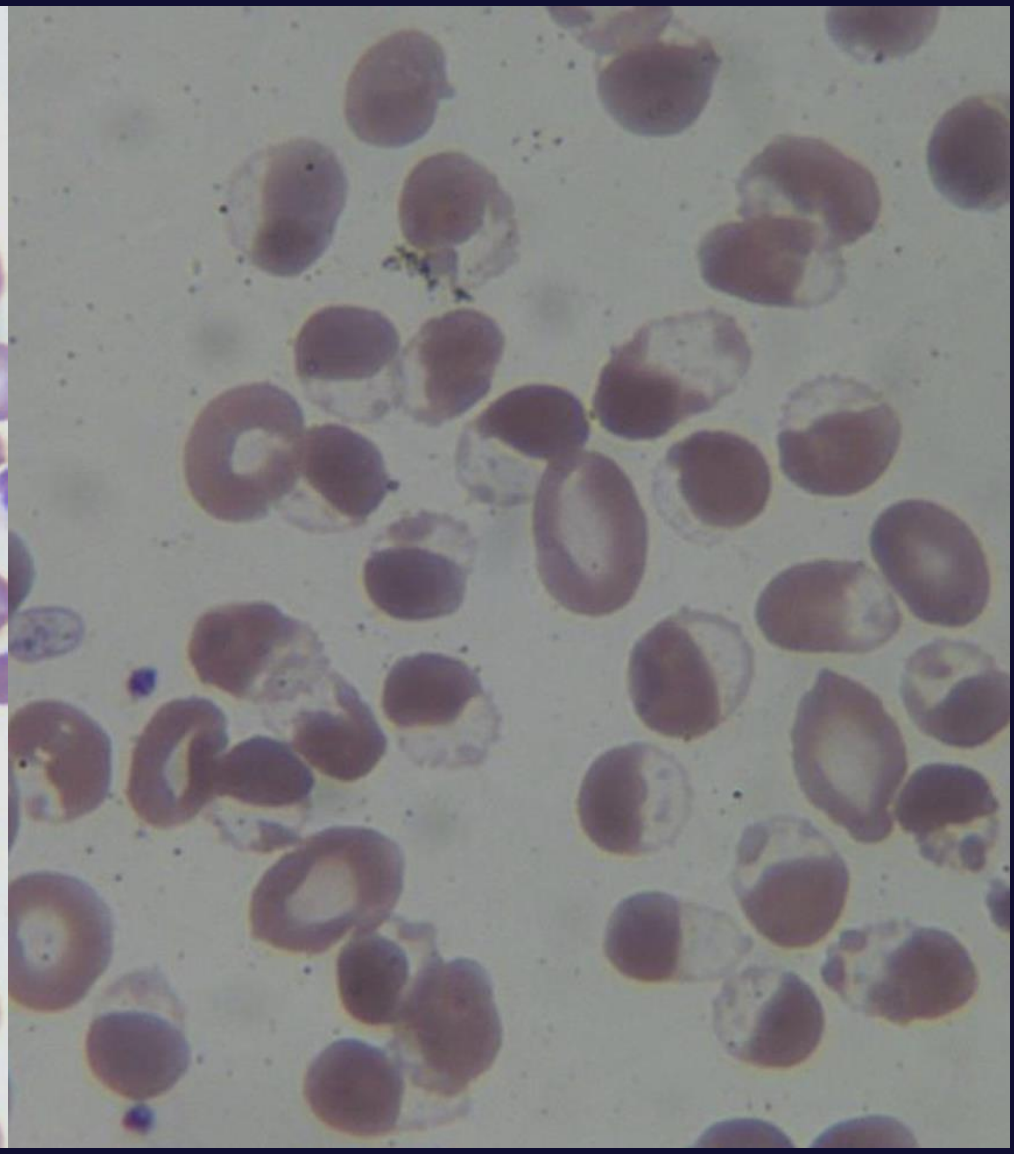
Male 26-year-old

URI symptoms 3 days

Fatigue with jaundice 2 days

Blood Smear





Dipen Chandrakant Patel, ASH image bank

G6PD Deficiency with Acute Hemolysis

X link recessive

Complication

- Hyperkalemia -> arrhythmia
- Hemoglobinuria -> ATN
- Heart Failure

Prevent Hemolysis in G6PD Def

Fava bean

Infection

Table 1 Drugs To Be Avoided by G6PD-Deficient Patients[16,19]

- Diaminodiphenyl sulfone (Dapsone)
- Flutamide (Eulexin)
- Furazolidone (Furoxone)
- Isobutyl nitrite
- Methylene blue
- Niridazole (Ambilhar)
- Nitrofurantoin (Furadantin)
- Phenazopyridine (Pyridium)
- Primaquine
- Rasburicase (Elitek)
- Sulfacetamide
- Sulfanilamide
- Sulfapyridine

Table 2 Drugs To Be Used With Caution in Therapeutic Doses for Patients With G6PD Deficiency (Without Nonspherocytic Hemolytic Anemia)[16,19]

- Acetaminophen (Tylenol)
- Acetylsalicylic acid (aspirin)
- Antazoline (Antistine)
- Antipyrine
- Ascorbic acid (vitamin C): intravenous doses only reported
- Benzhexol (Artane)
- Chloramphenicol
- Chlorguanidine (Proguanil, Paludrine)
- Chloroquine
- Colchicine
- Diphenyldramine (Benadryl)
- Glyburide (glibenclamide, Diabeta, Glynase)
- Isoniazid
- L-Dopa
- Quinine
- Streptomycin
- Sulfacytine
- Sulfadiazine
- Sulfaguanidine
- Sulfamethoxazole (Gantanol)
- Sulfisoxazole (Gantrisin)
- Trimethoprim
- Tripelennamine (Pyribenzamine)
- Vitamin K

Pharmacy and Therapeutics, *40*(9), 572.

Case 3

Male 48-year-old

Chronic constipation for 3 weeks

PE: moderately pale, no jaundice

Per rectal exam: no rectal mass, yellow feces

CBC

CBC / EDTA blood				
RBC	3.39	10^6/uL	L	4.00 - 5.20
HGB	8.6	g/dL	L	12.0 - 14.3
HCT	28.1	%	L	36.0 - 47.7
MCV	82.9	fL	-	80.0 - 97.8
MCH	25.4	pg	-	25.2 - 32.0
MCHC	30.6	g/dL	-	29.9 - 34.3
RDW	16.6	%	H	11.9 - 14.8
WBC	6.18	10^3/uL	-	4.60 - 10.60
PLT	138	10^3/uL	L	173 - 383
MPV	8.6	fL	L	8.7 - 12.5
NE%	57.6	%	-	43.7 - 70.9
LY%	32.5	%	-	20.1 - 44.5
MO%	8.1	%	-	3.4 - 9.8
EO%	1.6	%	-	0.7 - 9.2
BA%	0.2	%	-	0.0-2.6
NRBC	0.0	/100 WBC	-	

Anemia

Size

การติดสี

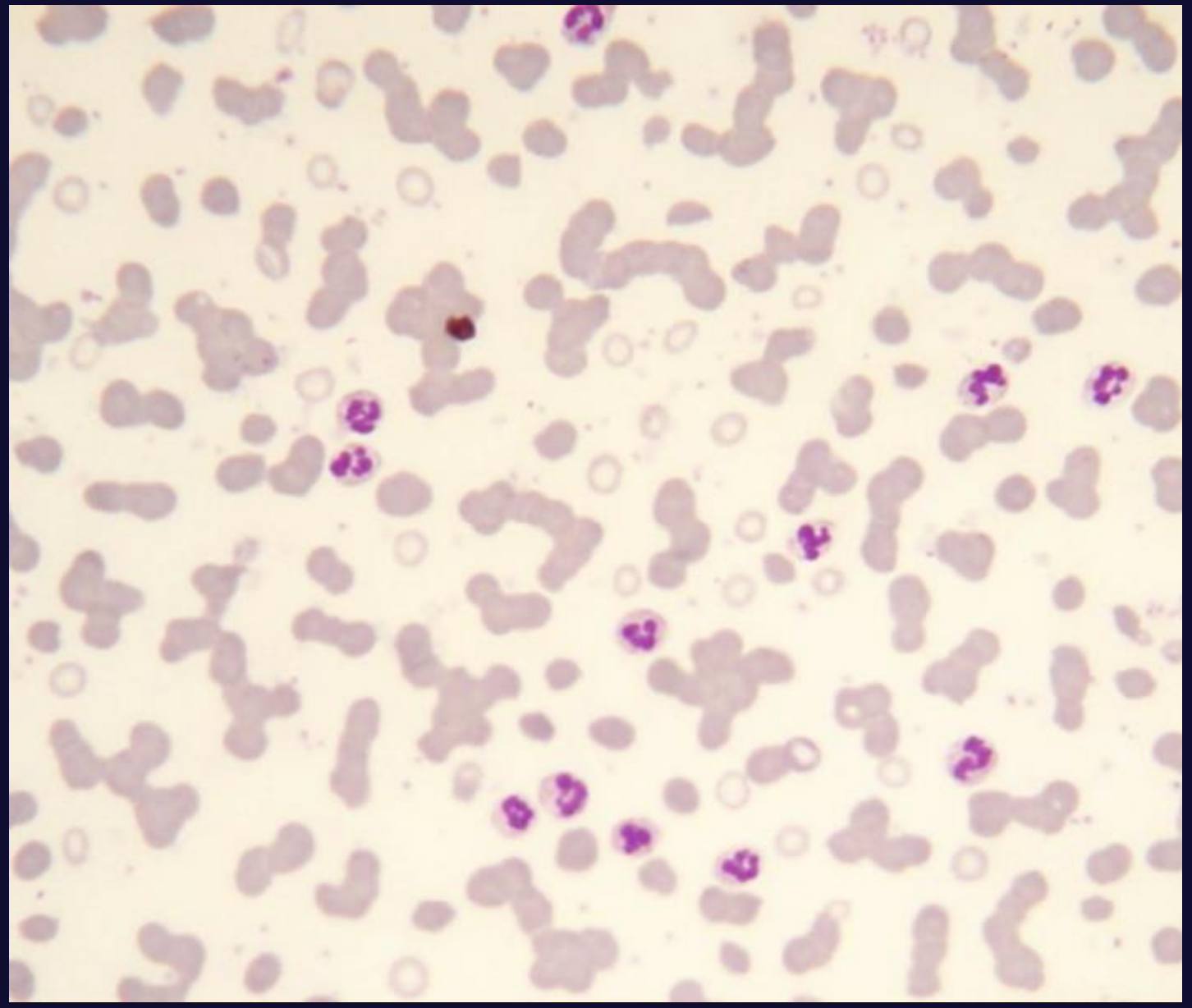
ความกลม

Anisocytosis

การทำงานของไขกระดูกด้านอื่น

หน้าที่หลักของไขกระดูก

Blood Smear



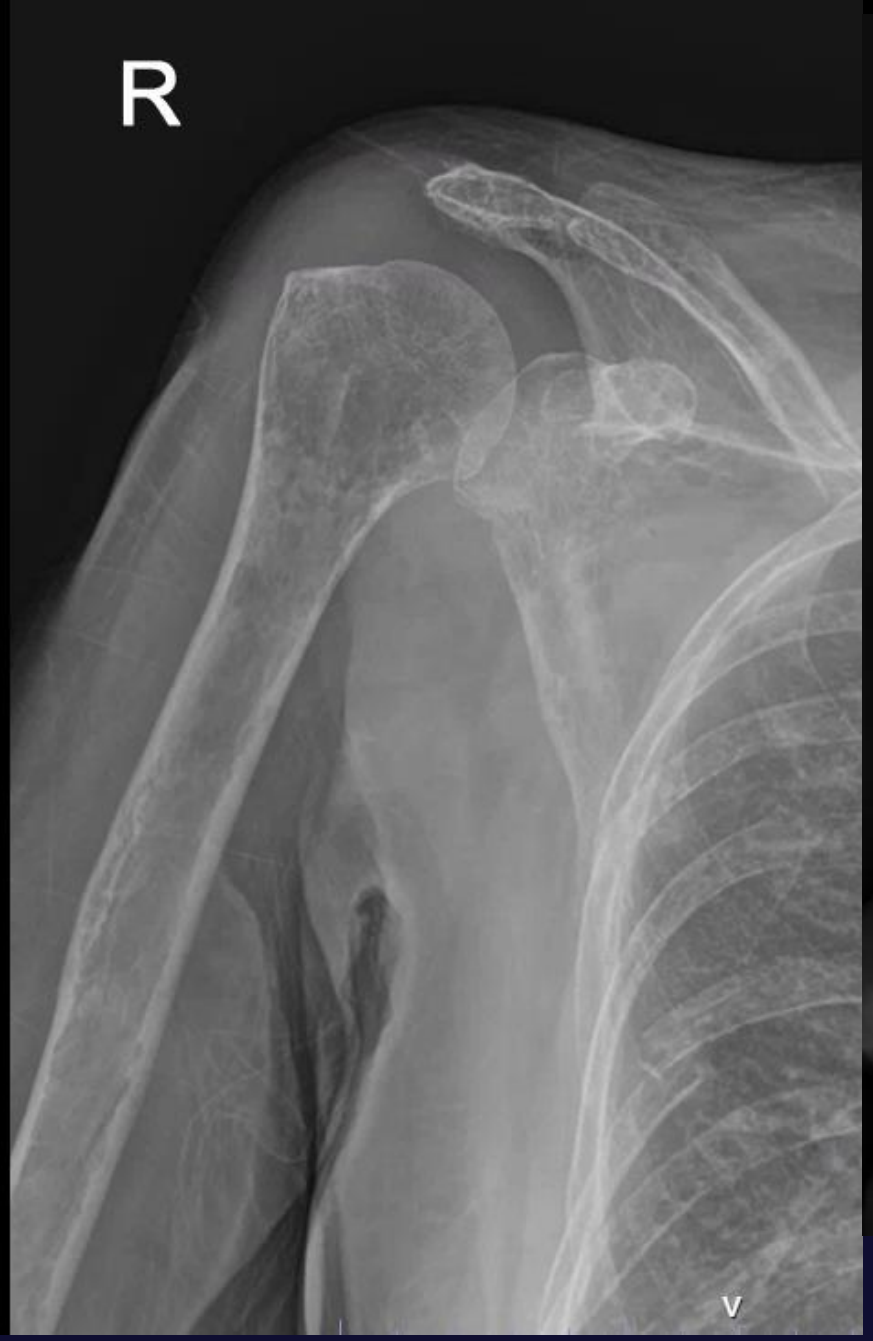
Rouleaux formation

Hyperglobulinemia

- Monoclonal
- Polyclonal

Calcium 13 mg/dL

Cr 2.2 mg/dL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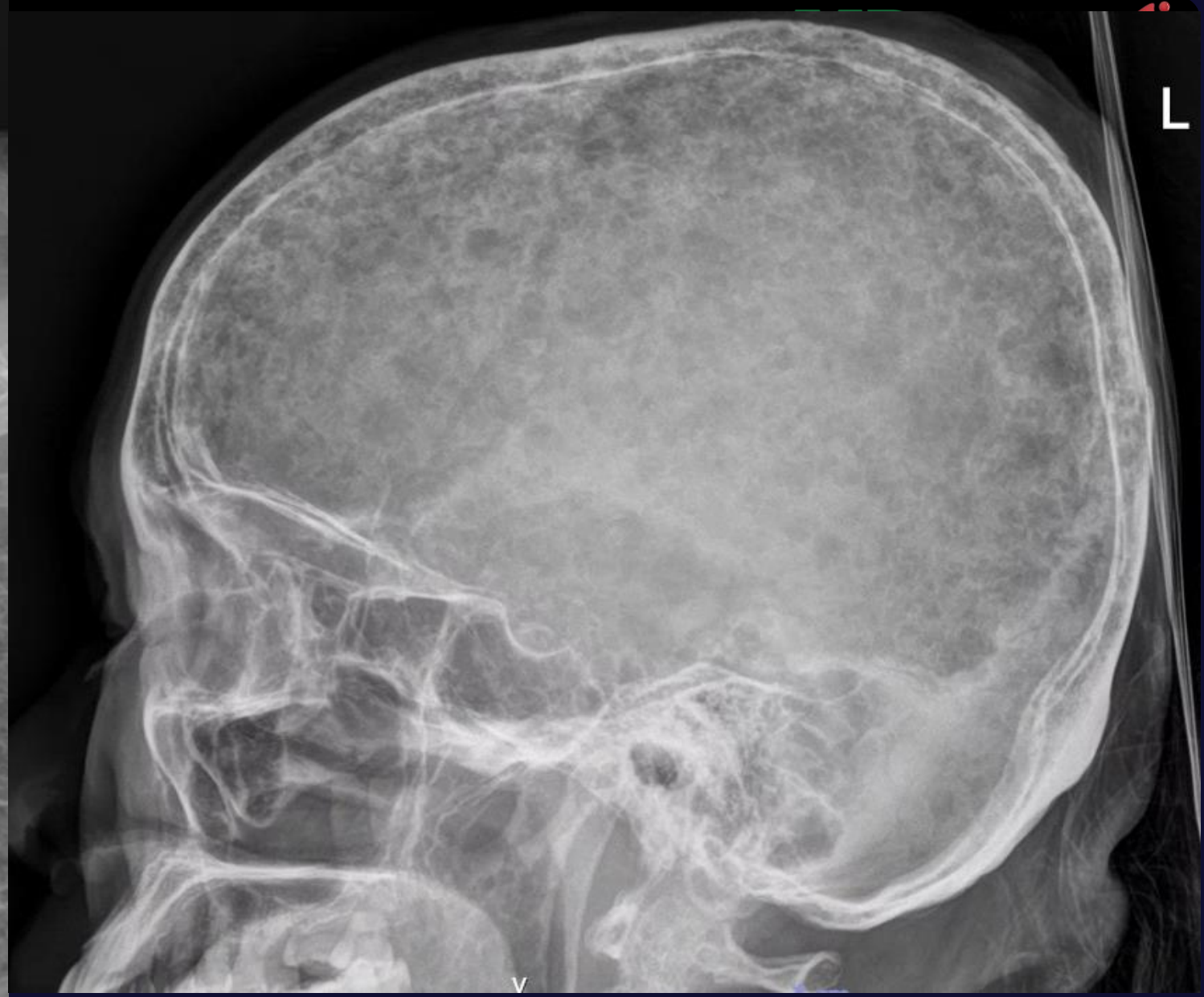
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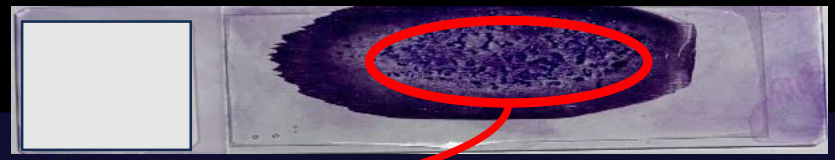
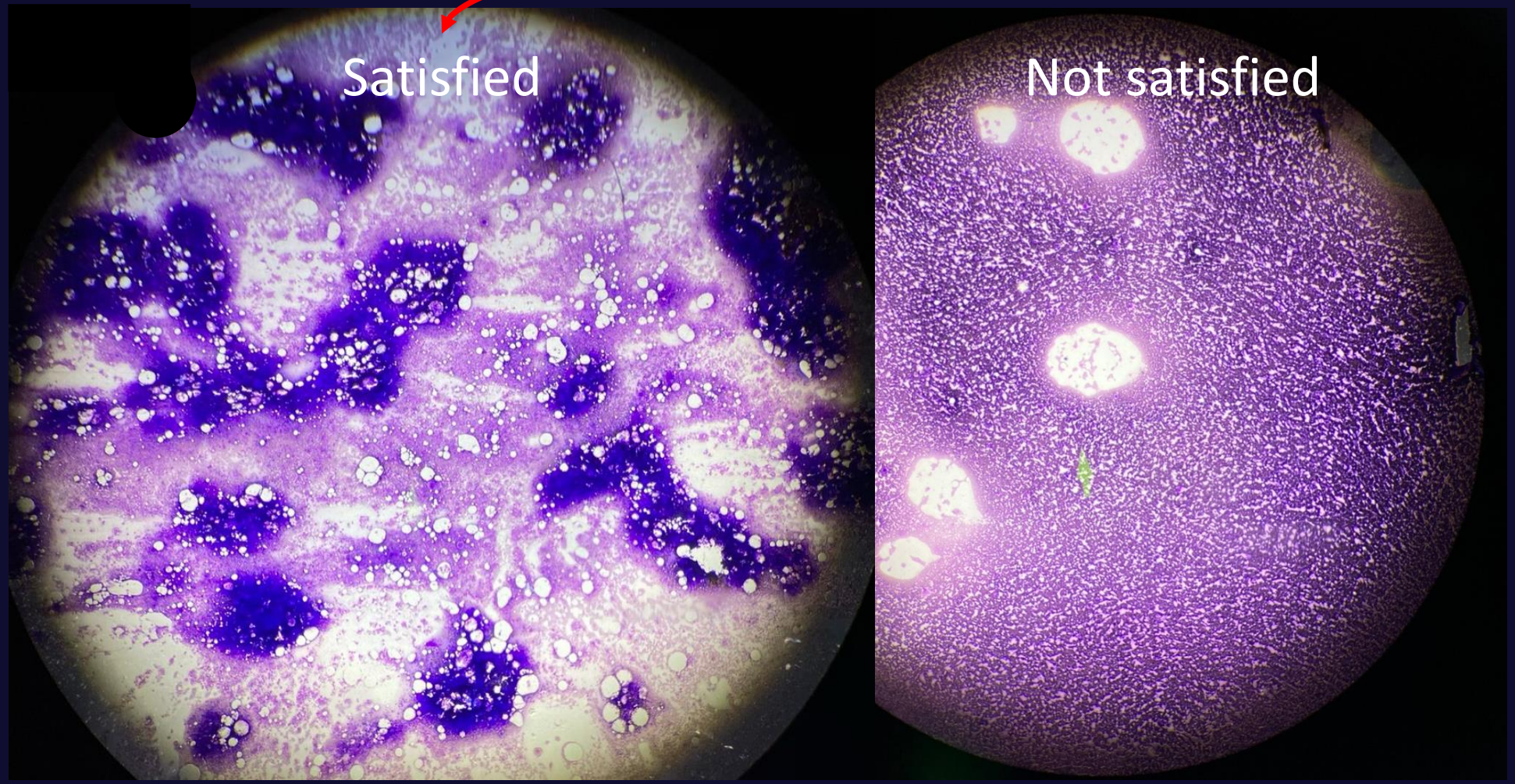
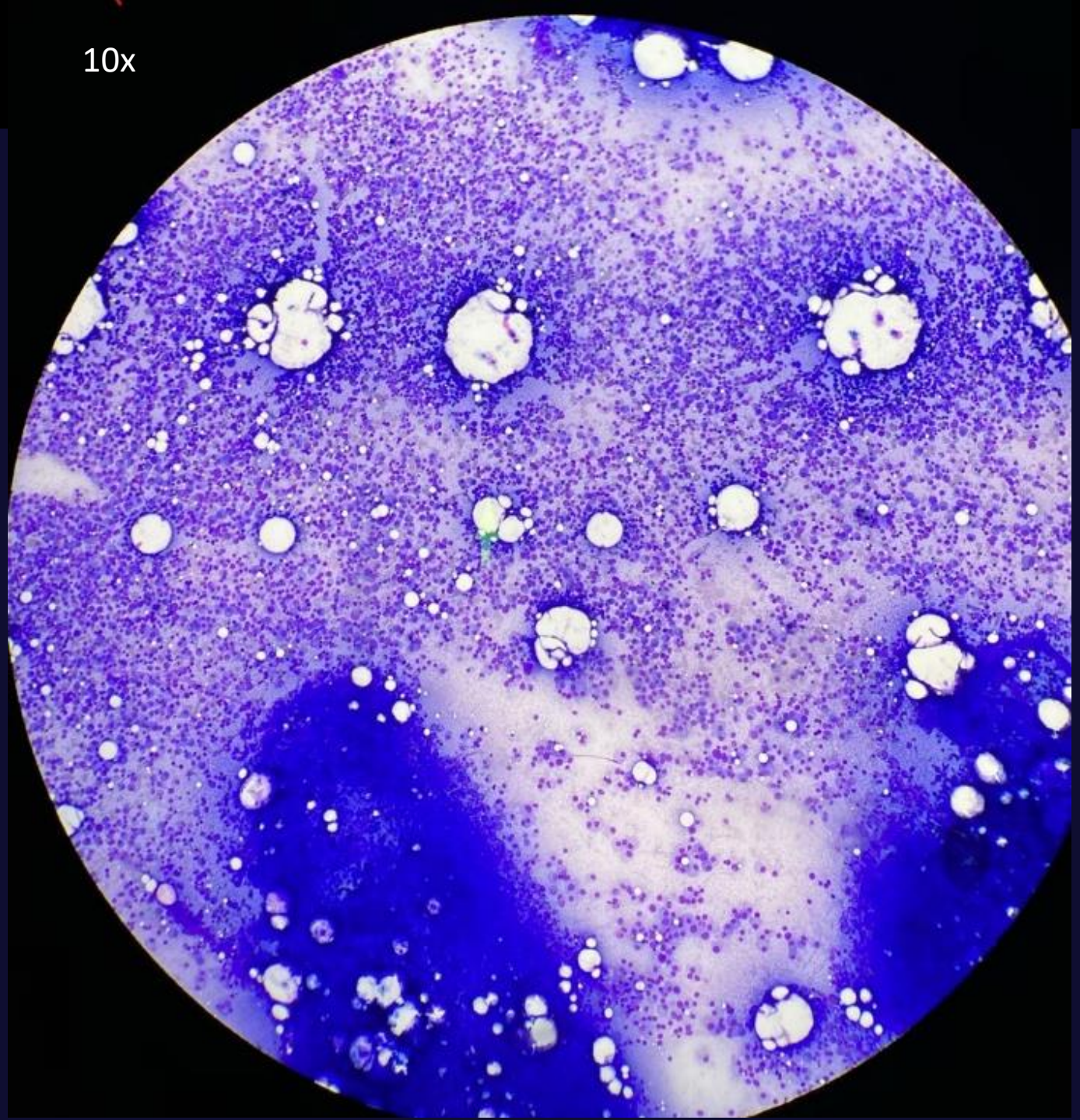
Bone Marrow Aspiration

- Cellularity : expected% =100-age(minimum 30%)
- Megakaryocyte : 5-10/thick part of particle
- M:E ratio = 3-5:1 (myeloid > erythroid)
- Myeloblast < 5%
- Lymphocyte < 20%
- Plasma cell < 5%
- RE cell < 1-2%

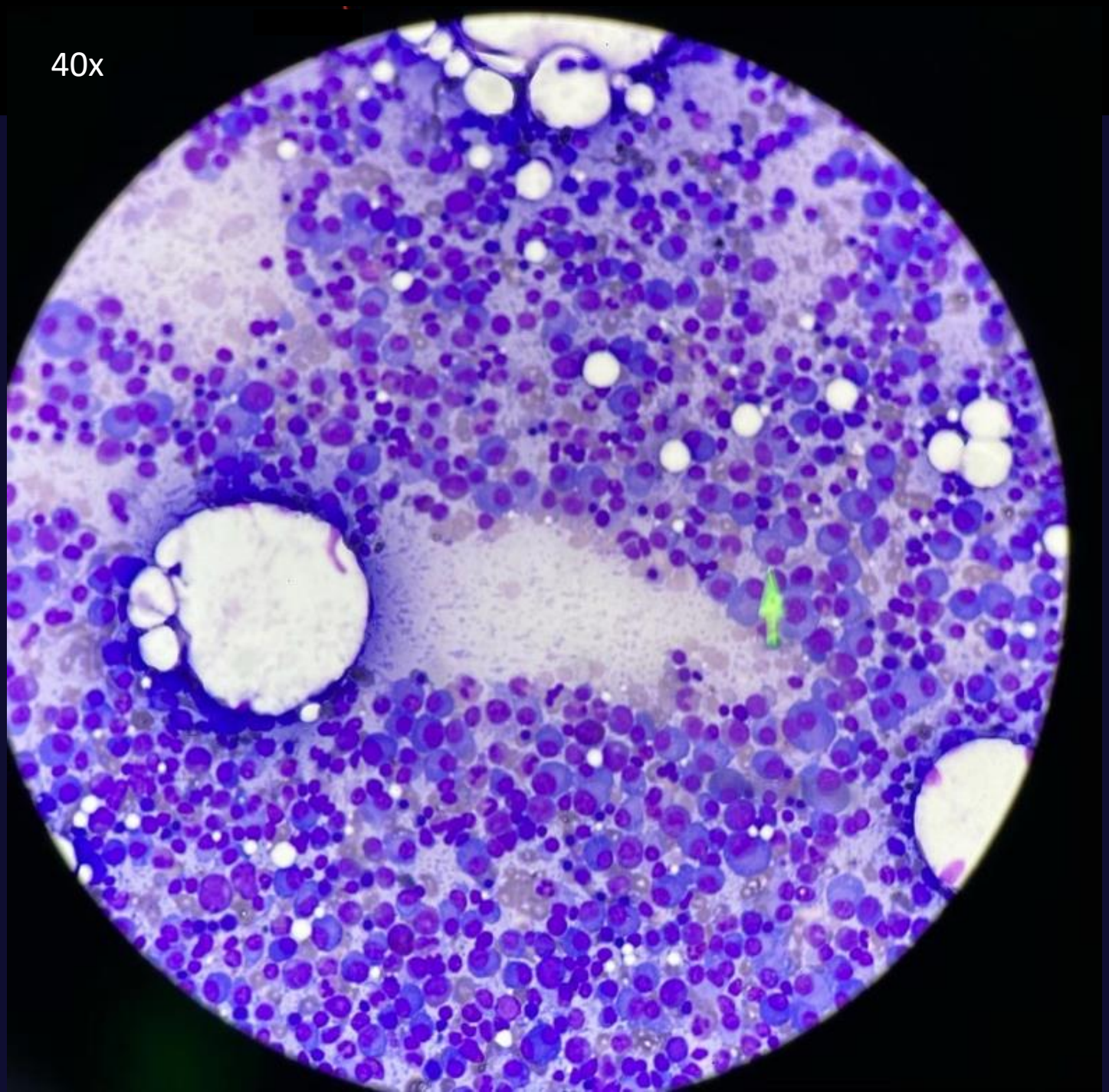


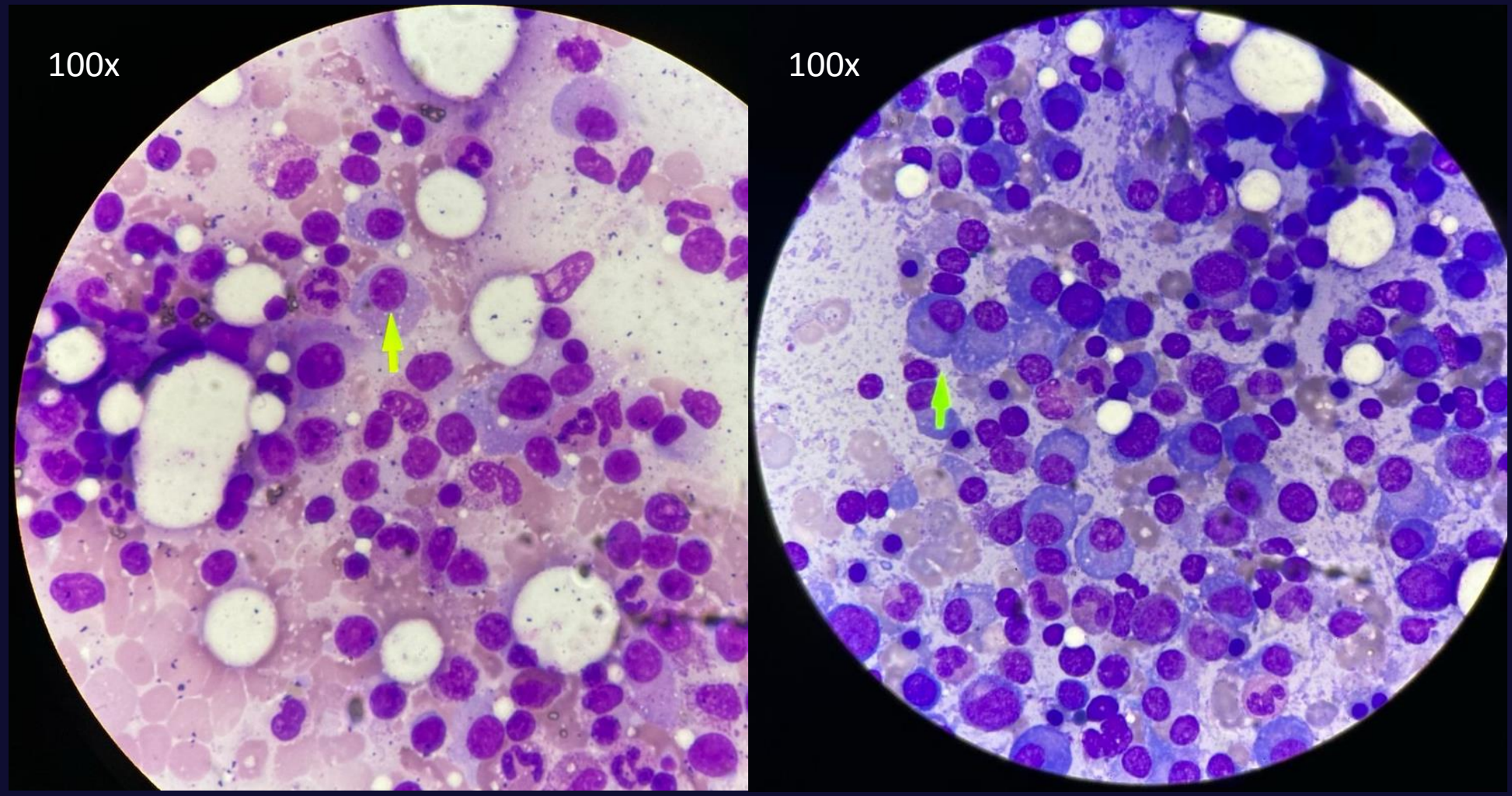

Satisfied
Not satisfied

10x

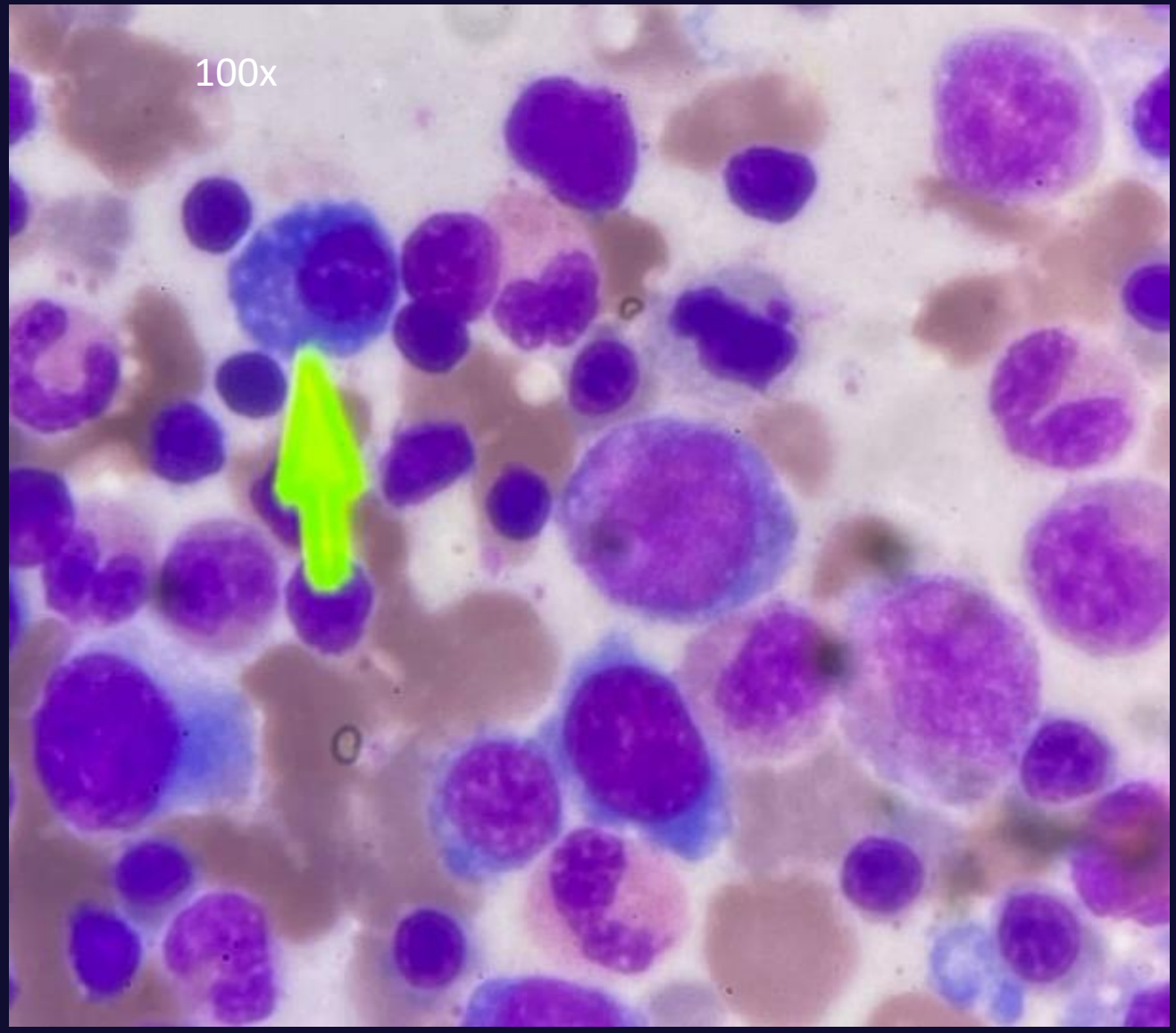


48-year-old




100x
100x

Normal Plasma Cell



Satisfied marrow

Hypercellularity 2+

Normal megakaryocyte

Decrease myeloid 2+

Decrease erythroid 2+

Plasma cell 70% with young and bizarre morphology

Imp: multiple myeloma

Presentation of MM

CRAB

Plasmacytoma

Recurrent Infection

AL amyloidosis

Cryoglobulinemia type I

Hyperviscosity syndrome

POEMS

Mandatory major criteria	1. Polyneuropathy (typically demyelinating)
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3. Castleman disease[a]
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid,[b] pituitary, gonadal, parathyroid, pancreatic[b])
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia[c]
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} values

Abbreviation: POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes.
The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present.

American Journal of Hematology, *94*(7), 812–827

Management

Incurable disease

Specific treatment

- Bortezomib/IMiDs/Anti-CD38 based regimen plus steroid
- Autologous stem cell transplantation

Skeletal prevention

- Bisphosphanate monthly x2 years

Management

Infection

- Influenza vaccine
- Pneumococcal vaccine
- HBV prophylaxis
- Herpes prophylaxis: acyclovir
- PCP prophylaxis: cotrimoxazole

Thromboprophylaxis

- IMPEDE score
- SAVED score (IMiDs)

Markedly hypercellularity bone marrow

Normal cell character

- Myeloproliferative neoplasm(CML, PV, ET) but abnormal megakaryocyte
- Reactive: erythroid hyperplasia(blood loss, hemolysis) leukemoid reaction

Abnormal cell character

- Acute myeloid leukemia
- Acute lymphoblastic leukemia
- Chronic lymphocytic leukemia
- Multiple myeloma
- AML M6
- Myelodysplastic syndrome(MDS)
- Megaloblastic anemia

Markedly Hypocellularity

Aplastic anemia

Hypoplastic MDS

Hypoplastic PNH

Hypoplastic leukemia

Drug induced myelosuppression

Case 4

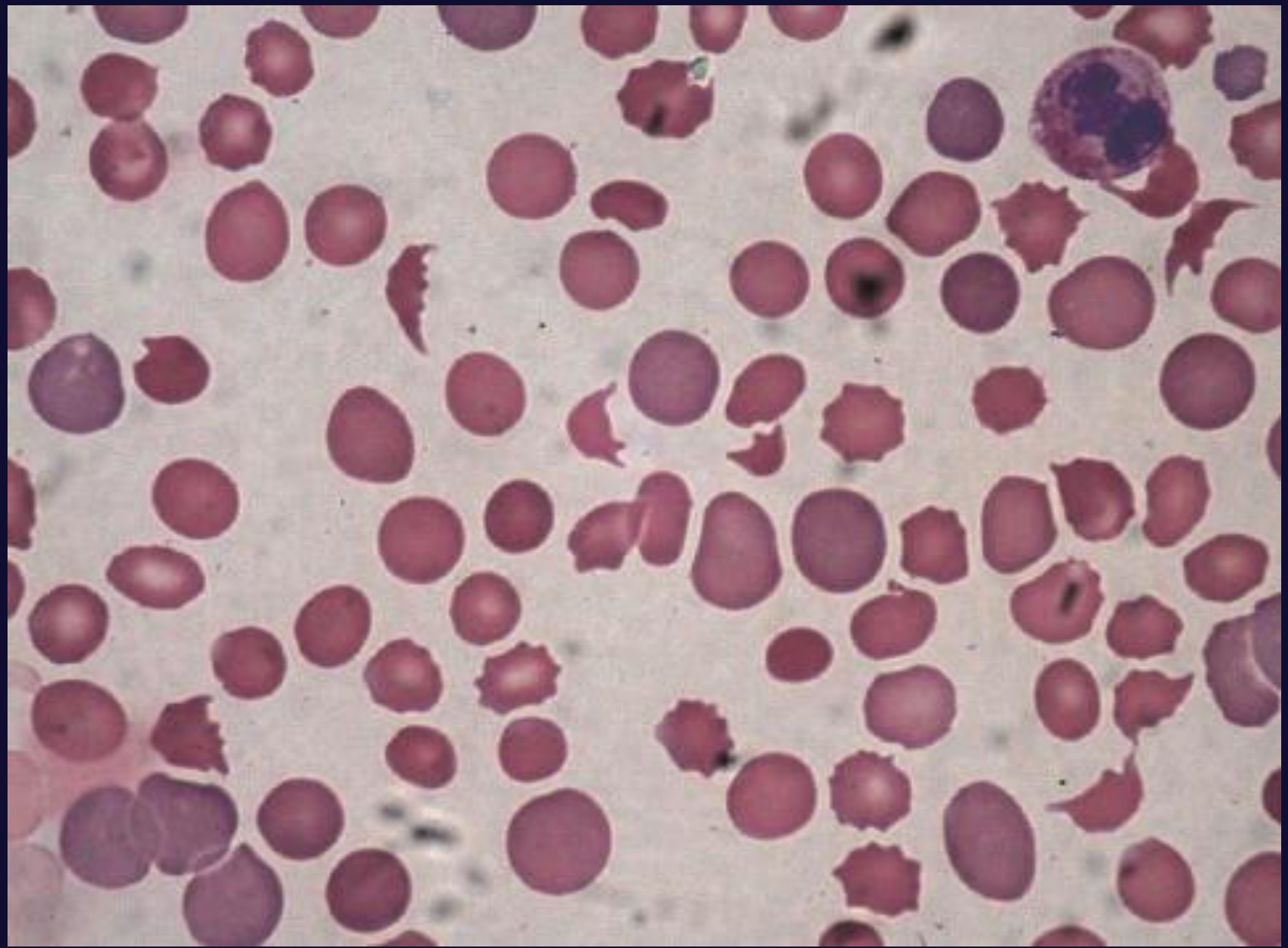
Female 35-year-old

Confusion 3 days

Fever without organ specific symptoms

Petechiae on both upper and lower extremities

Blood Smear



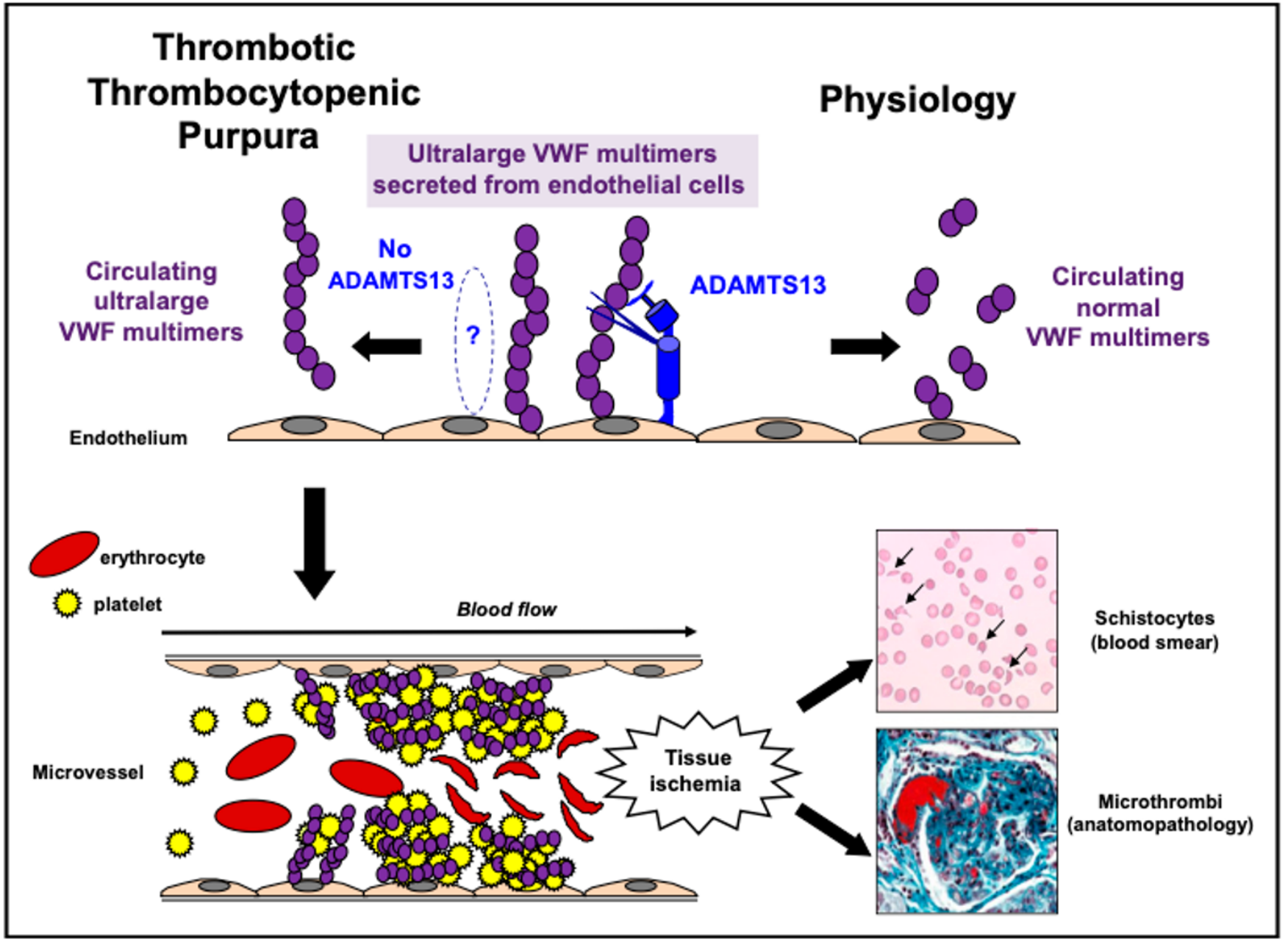
MAHA blood picture

- DIC
- HUS
- TTP

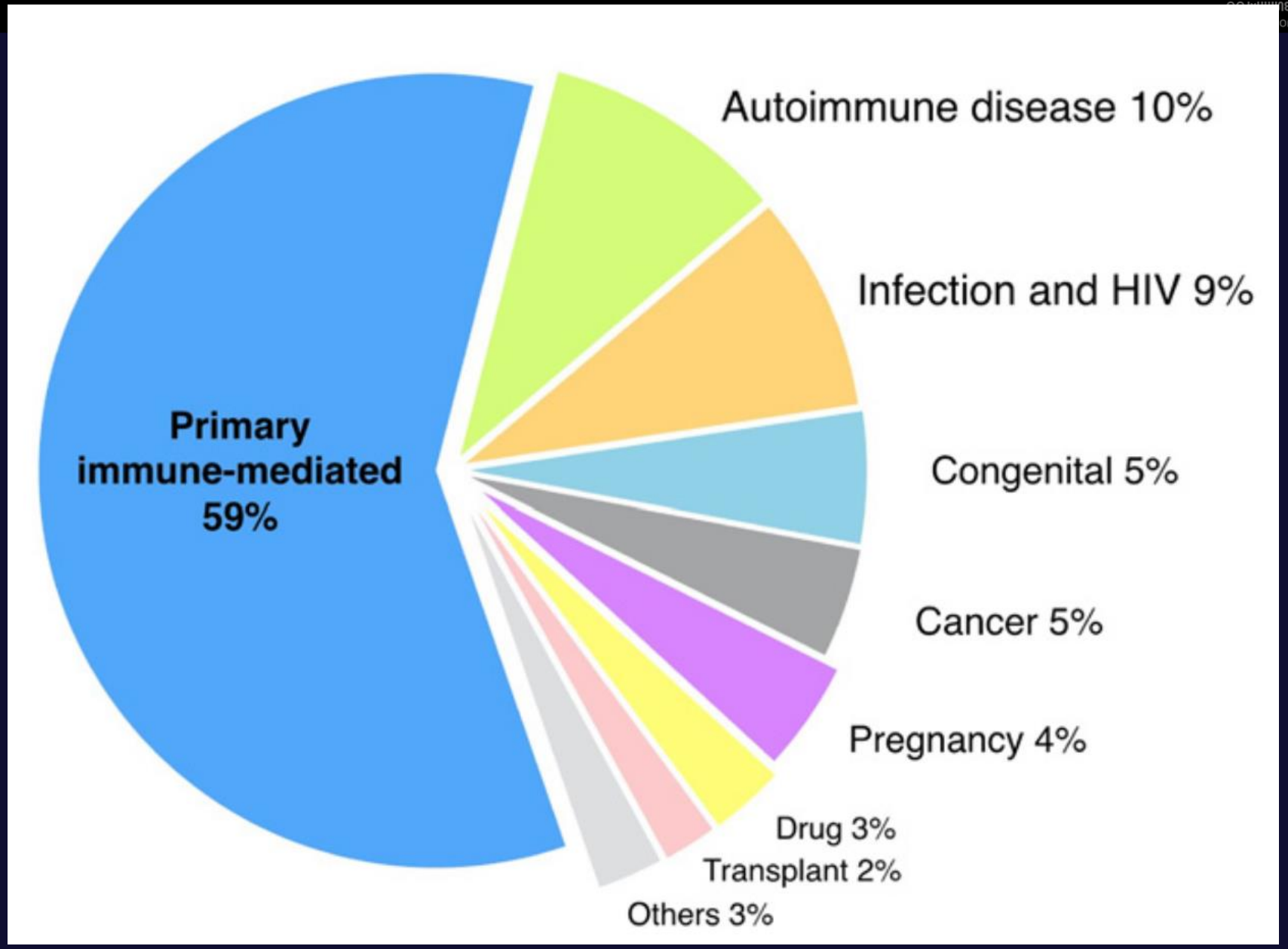
TTP = Absent of ADAMTS13 → TMA

Table 2. Clinical and laboratory findings in TTP[2-7,12]

	Frequency (%)
Clinical presentation, %	
MAHA with thrombocytopenia	100
Neurological abnormalities	39-80
Major	18-53
Minor	27-42
Fever	10-72
Gastrointestinal symptoms	35-39
Renal involvement	10-75
Classic pentad*	7
Laboratory findings	
Median platelet count, $\times 10^9$/L	10-17
Median creatinine, μmol/L	0.96-1.42
Median LDH, U/L	1107-1750
Median hematocrit, %	20-27



Hematology, *2018*(1), 530–538 *Blood*, *129*(21), 2836–2846



Blood, *129*(21), 2836–2846

TTP Treatment

Plasma exchange:

1-1.5x plasma volume once daily until plt >150k x 2 days

High dose steroid: IV methylprednisolone, Dexamethasone

Rituximab

Caplacizumab (inhibit platelet GPIb – VWF A1)

Intramedullary Hemolysis

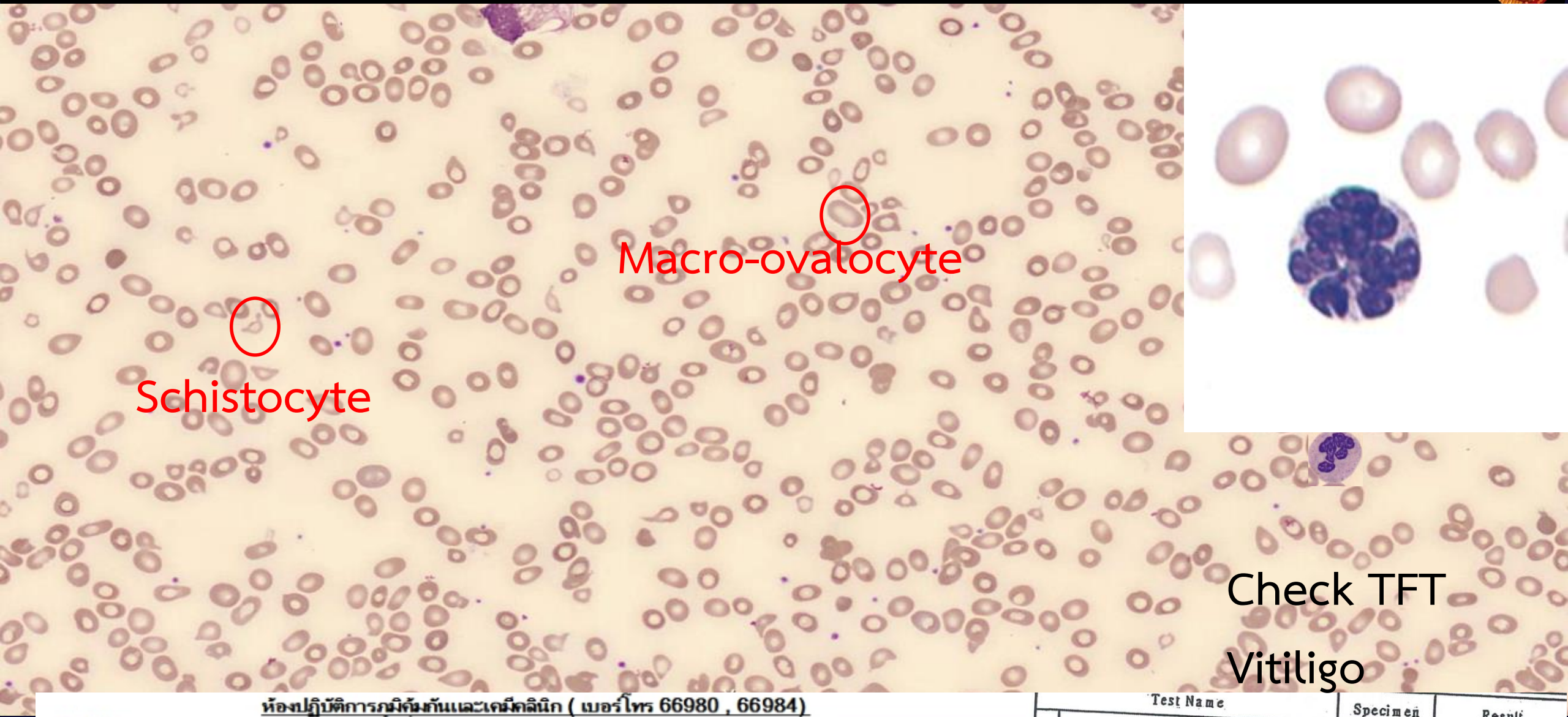
Test Name/Specimen Type	Result	Unit		Reference V
CBC / EDTA blood				
RBC	1.86	10^6/uL	L	4.00 - 5.20
HGB	7.0	g/dL	LL	12.0 - 14.3
HCT	20.7	%	L	36.0 - 47.7
MCV	111.3	fL	H	80.0 - 97.8
MCH	37.6	pg	H	25.2 - 32.0
MCHC	33.8	g/dL	-	29.9 - 34.3
RDW	23.7	%	H	11.9 - 14.8
WBC	5.18	10^3/uL	-	4.60 - 10.60
PLT	89	10^3/uL	L	173 - 383
MPV	---	fL	-	8.7 - 12.5
Plt smear	Decreased		-	
NE%	50.0	%	-	43.7 - 70.9
LY%	41.0	%	-	20.1 - 44.5
MO%	0.0	%	L	3.4 - 9.8
EO%	4.0	%	-	0.7 - 9.2
BA%	0.0	%	-	0.0-2.6

BUN / Clot blood	10.3	mg/dL	-	6-20
CREATININE / Clotted Blood				
CREATININE, 32202	0.62	mg/dL	-	0.51-0.95
eGFR(CKD-EPI) age >=18	115.56	ml/min/1.73m2	-	
SODIUM / Clot blood	136	mEq/L	L	136-145
POTASSIUM / Clot blood	3.5	mEq/L	-	3.5-5
BICARBONATE / Clot blood	19.7	mEq/L	L	23-30
CHLORIDE / Clot blood	100	mEq/L	-	98-106
CHOLESTEROL / Clot blood	176	mg/dL	-	0-200
TOTAL PROTEIN / Clot blood	7.8	g/dL	-	6.6-8.7
ALBUMIN / Clot blood	4.8	g/dL	-	3.5-5.2
Globulin / Clot blood	3.0	g/dL	-	2.6-3.4
TOTAL BILIRUBIN / Clot blood	4.0	mg/dL	H	0.3-1.2
DIRECT BILIRUBIN / Clot blood	0.9	mg/dL	H	0-0.5

reti 1.5%, absolute reticulocyte count = 42780

LDH 6500

Pseudo-TMA



Check TFT

Vitiligo

ห้องปฏิบัติการภูมิคุ้มกันและเคมีคลินิก (เบอร์โทร 66980 , 66984)

Test Name/Specimen Type	Result	Unit		Reference Value
Vitamin B12 / Clotted blood	<50	pg/ml	-	197-771

	Test Name	Specimen	Result
1	Anti-parietal cell antibody	serum	40
2	Anti-intrinsic factor antibody	serum	Positive

Other Signs of B12 Deficiency

New England Journal of Medicine, 386(2), 172–172

Before

After

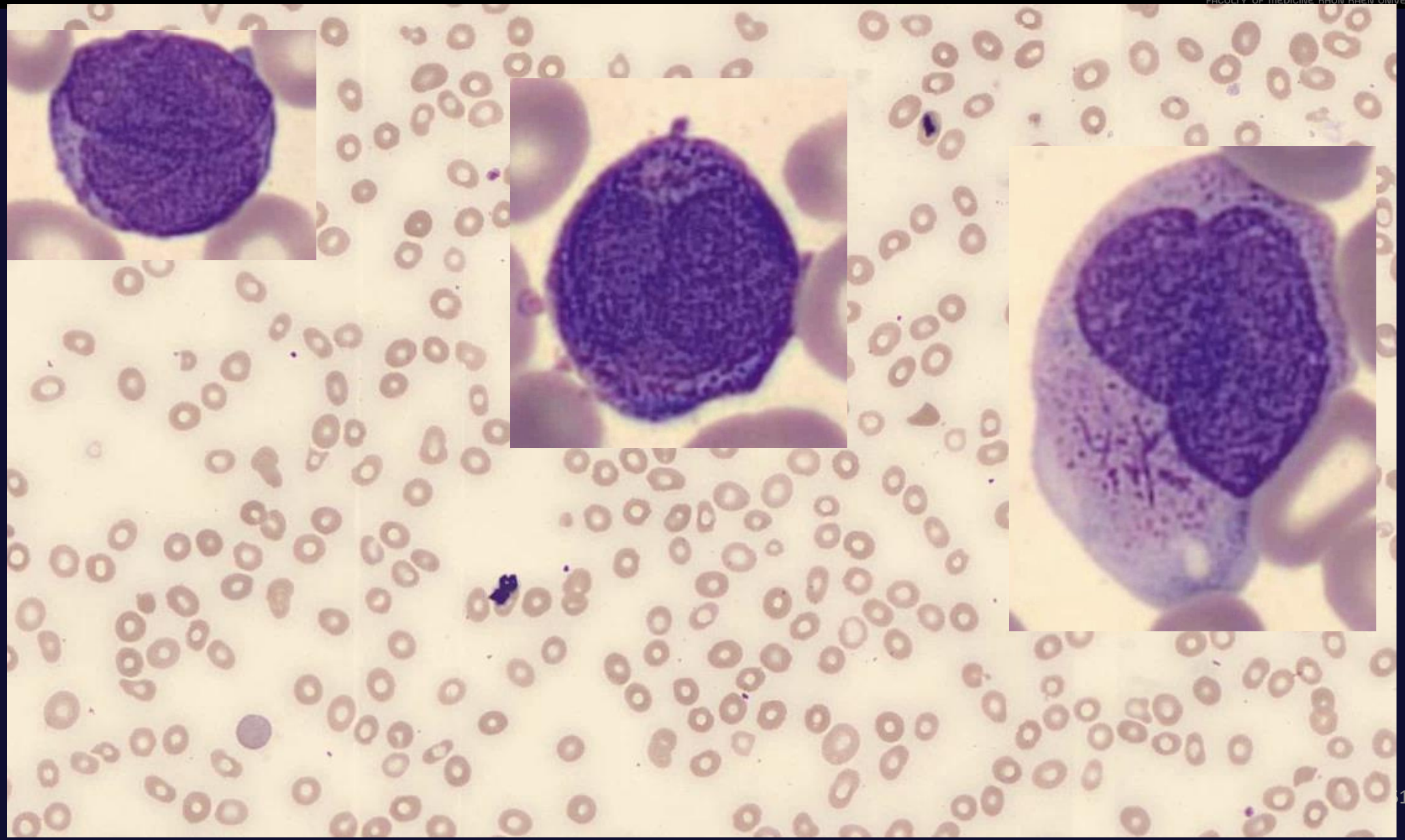
Case 5

Female 32-year-old

Bleeding per gum 5 days with anemic symptoms

Petechiae and deep ecchymosis both legs

Test Name/Specimen Type	Result	Unit		Reference Value
PT/INR / 3.2% Sodium citrate blood				
PT	14.1	sec	H	10.0 - 12.6
INR	1.25		-	
aPTT / 3.2% Sodium citrate blood				
aPTT	30.9	sec	-	26.3 - 38.5
APTT Ratio	0.95		-	
CBC /EDTA blood				
RBC	2.25	10^6/uL	L	4.00 - 5.20
HGB ตรวจสอบซ้ำแล้ว	5.9	g/dL	LL	12.0 - 14.3
HCT	18.0	%	L	36.0 - 47.7
MCV	80.0	fL	-	80.0 - 97.8
MCH	26.2	pg	-	25.2 - 32.0
MCHC	32.8	g/dL	-	29.9 - 34.3
RDW	19.1	%	H	11.9 - 14.8
WBC ตรวจสอบซ้ำแล้ว	1.93	10^3/uL	LL	4.60 - 10.60
PLT ตรวจสอบซ้ำแล้ว	11	10^3/uL	LL	173 - 383
MPV	—	fL	-	8.7 - 12.5
Plt smear	Decreased		-	
NE%	20.5	%	L	43.7 - 70.9
LY%	41.8	%	-	20.1 - 44.5
MO%	20.9	%	H	3.4 - 9.8
EO%	16.8	%	H	0.7 - 9.2
BA%	0.0	%	-	0.0 - 2.6

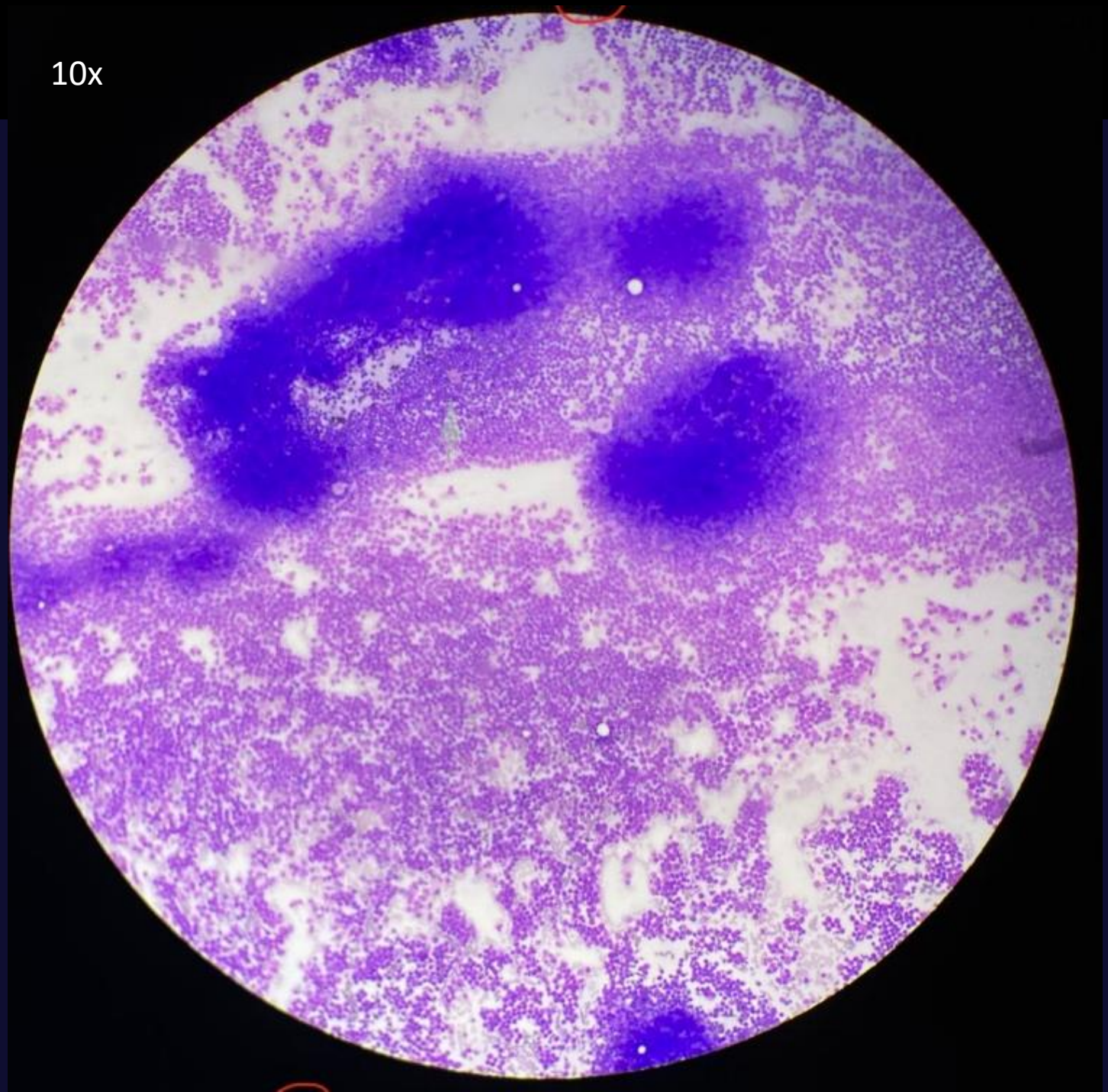


Acute Promyelocytic Leukemia (AML-M3)

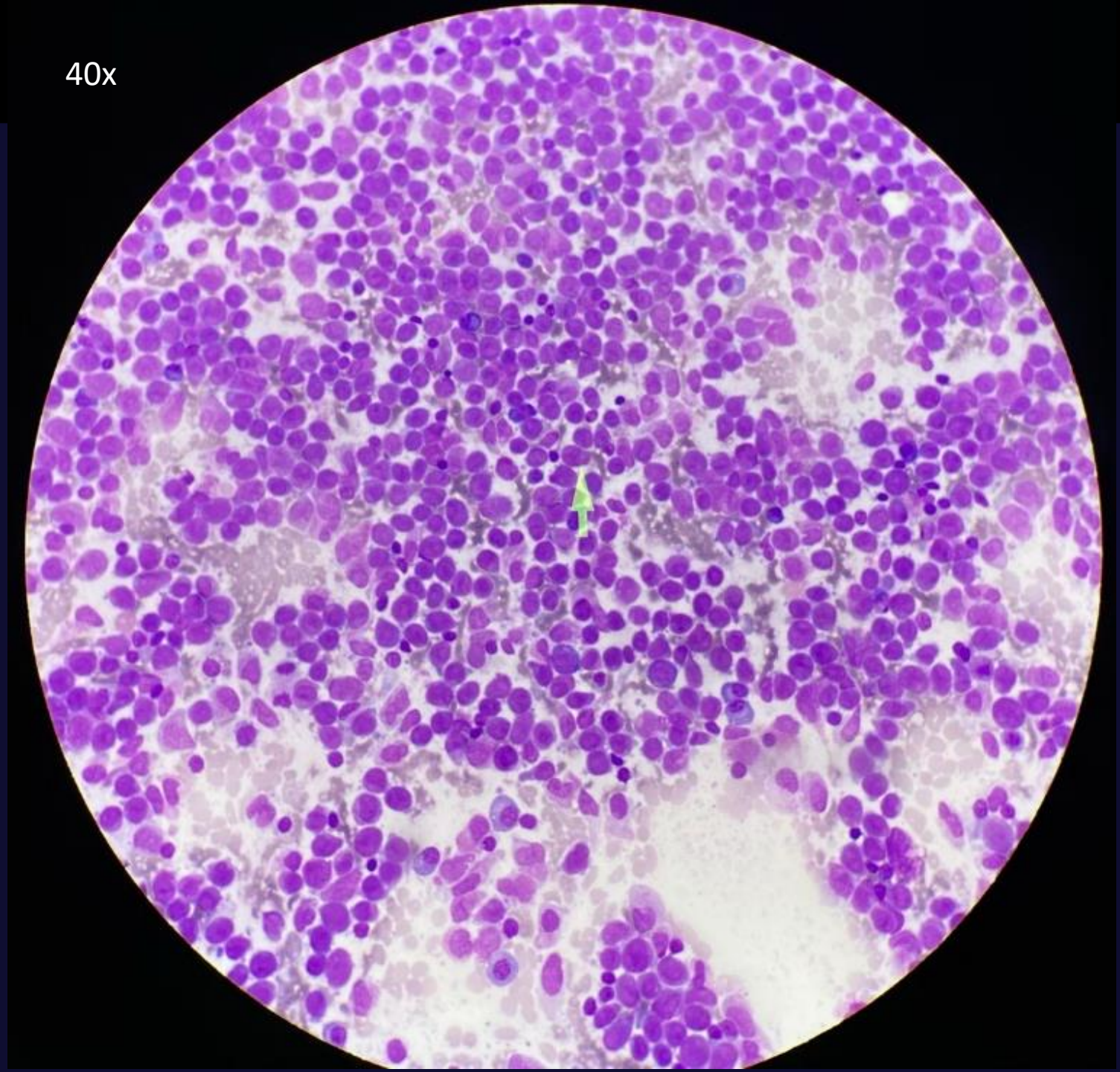
Investigation

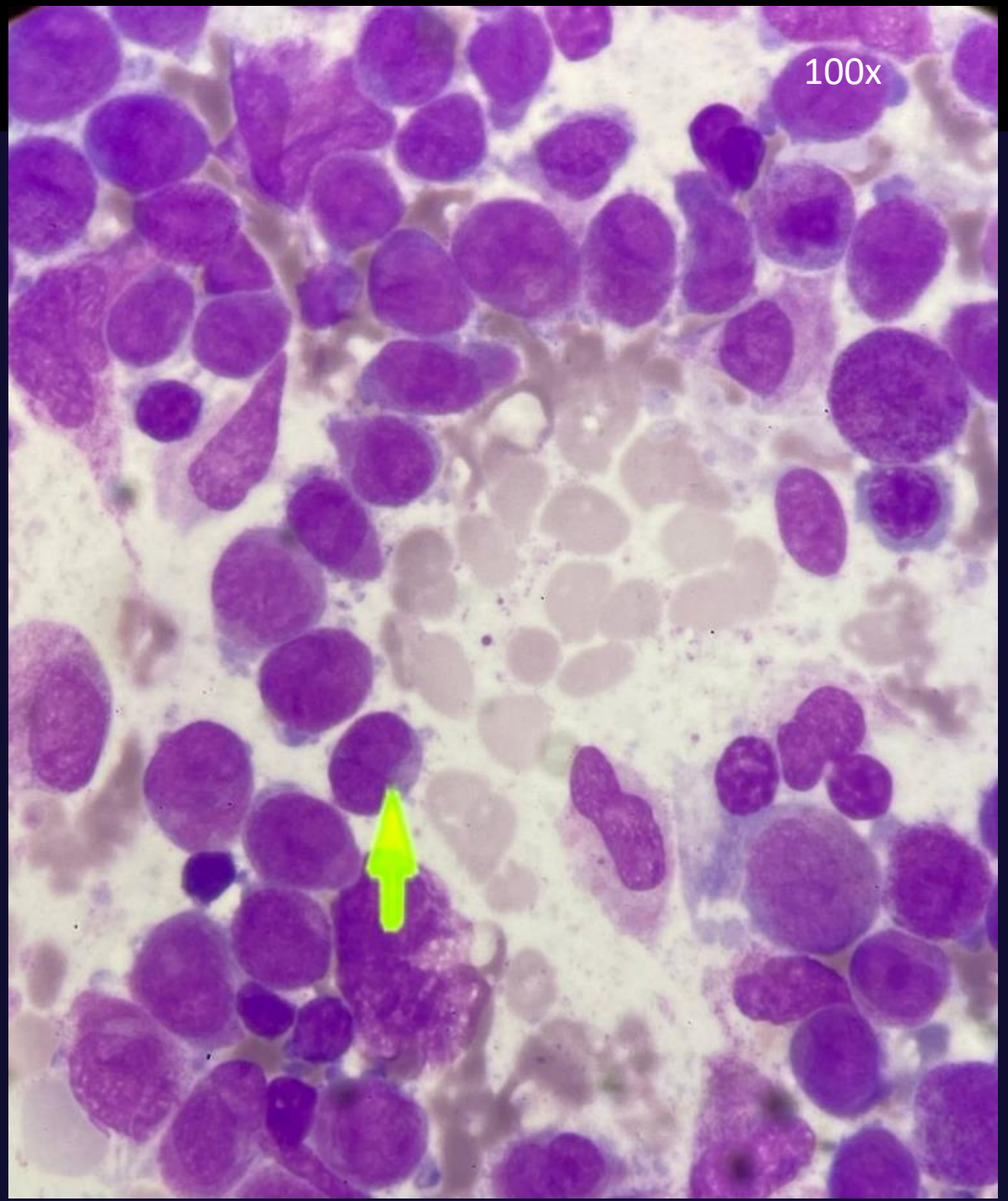
- Bone marrow aspiration and biopsy
- Flow cytometry for leukemia
- BM FISH for t(15;17) Blood PCR for PML-RARA fusion gene

10x



40x




100x

Satisfied marrow

Hypercellularity 3+

Decrease megakaryocyte 3+

Decrease myeloid 3+

Decrease erythroid 3+

Diffuse infiltration of abnormal promyelocyte with dense heavy granule 90%

Imp: acute promyelocytic leukemia (AML-M3)

Acute Promyelocytic Leukemia (AML-M3)

10-yr survival rate 77%

Treatment

All-trans retinoic acid based (ATRA)

+ Idarubicin or Arsenic trioxide (ATO)

Prevent differentiation syndrome with dexa 10 mg iv q 12 hr in WBC >5,000-10,000

DIC management

Red cell: LPRC keep Hb >8 g/dL

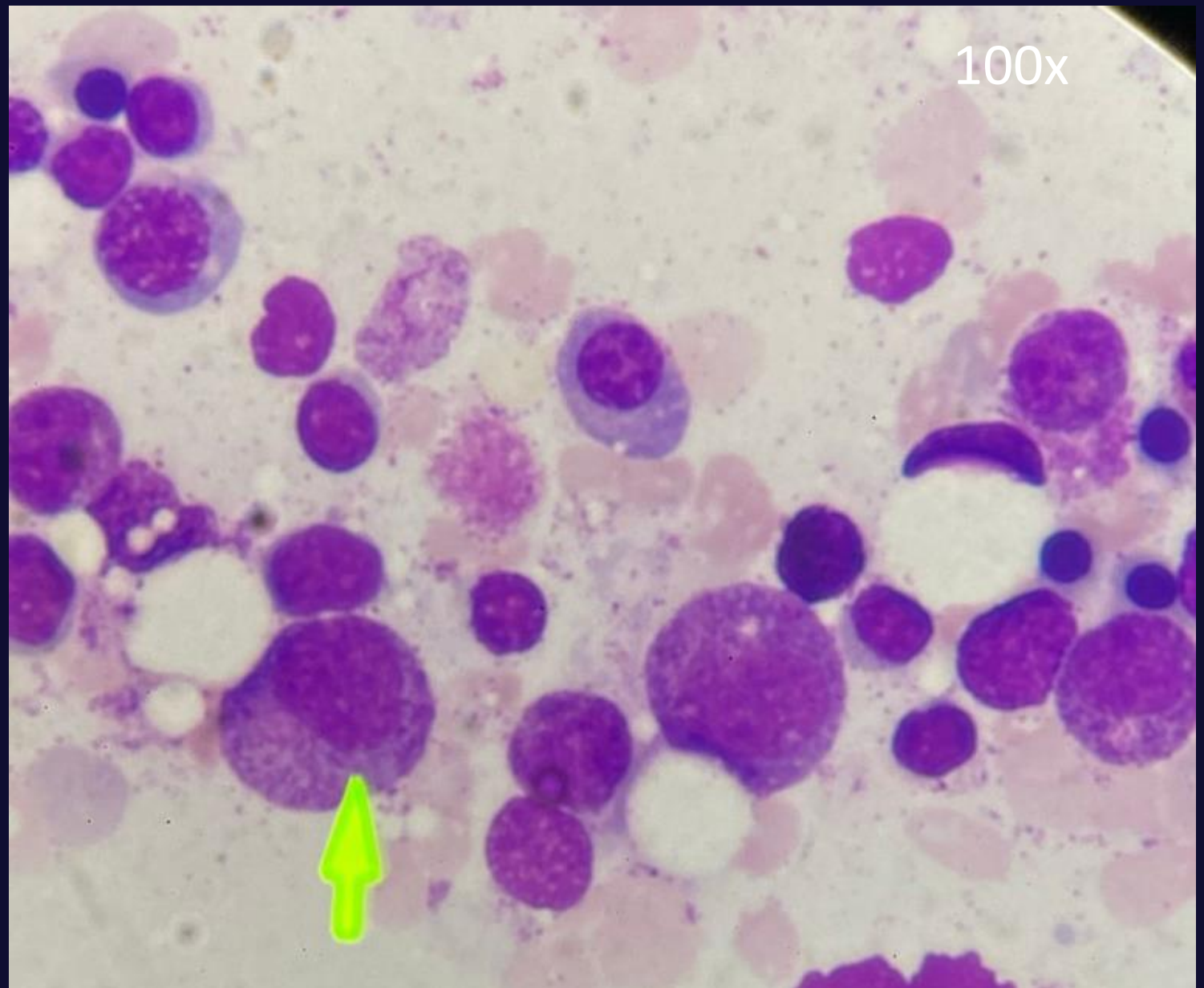
Platelet: LPPC, SDP keep >50 $x10^9$/L

Fibrinogen: Cryoprecipitate keep >150 mg/dL

Coag factor: FFP keep INR <1.5

Blood, *133*(15), 1630–1643

Agranulocytosis (normal promyelocyte)

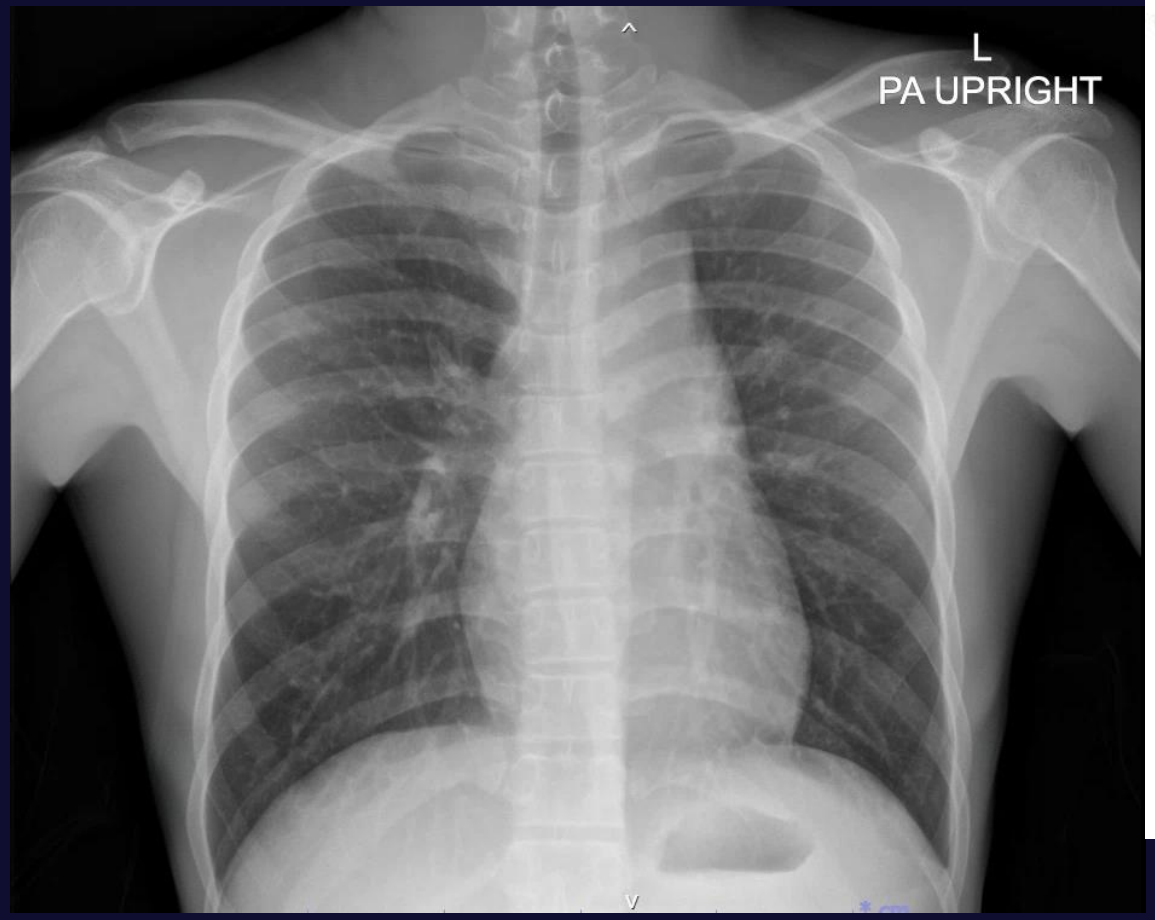


Hypocellular

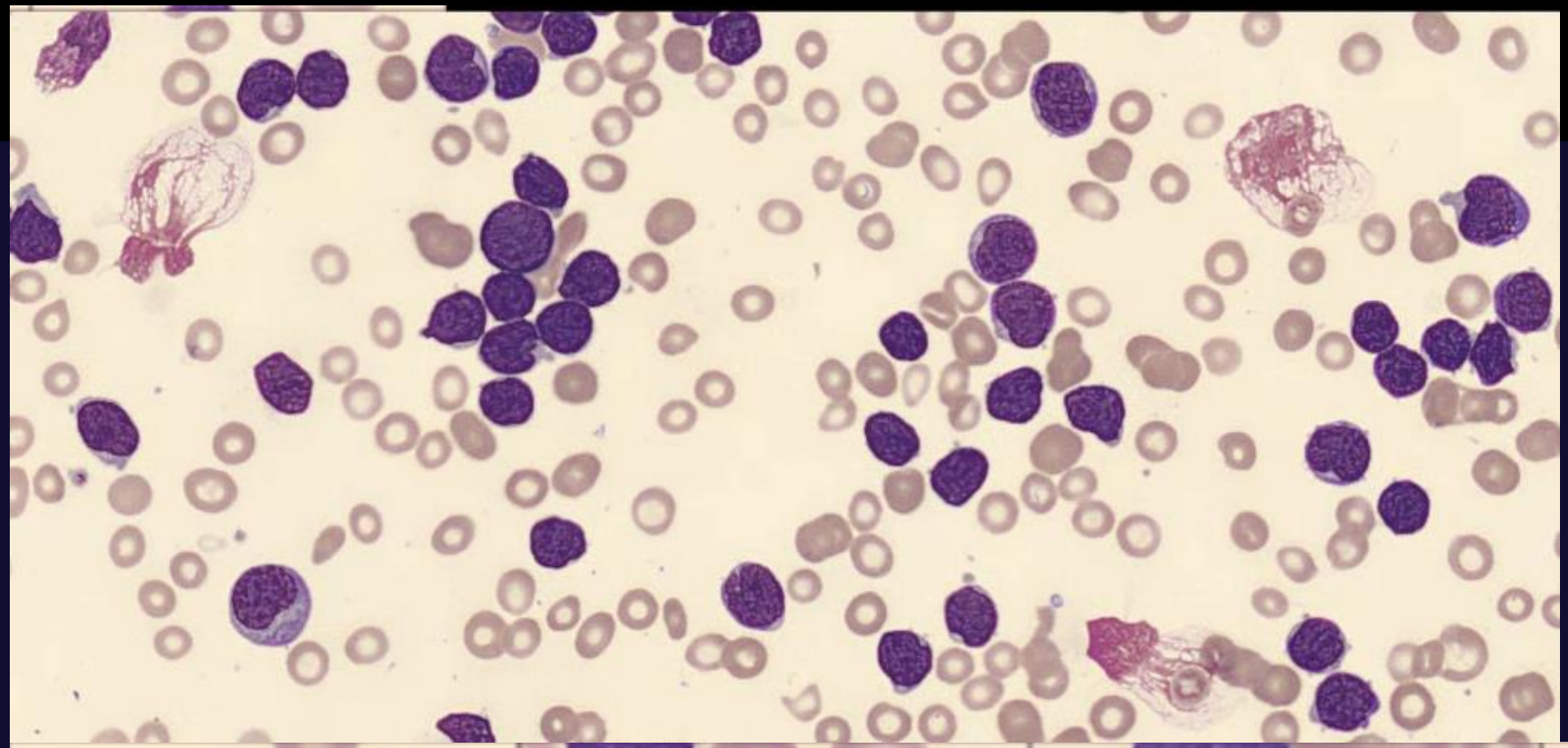
Case 6

Male 35-year-old

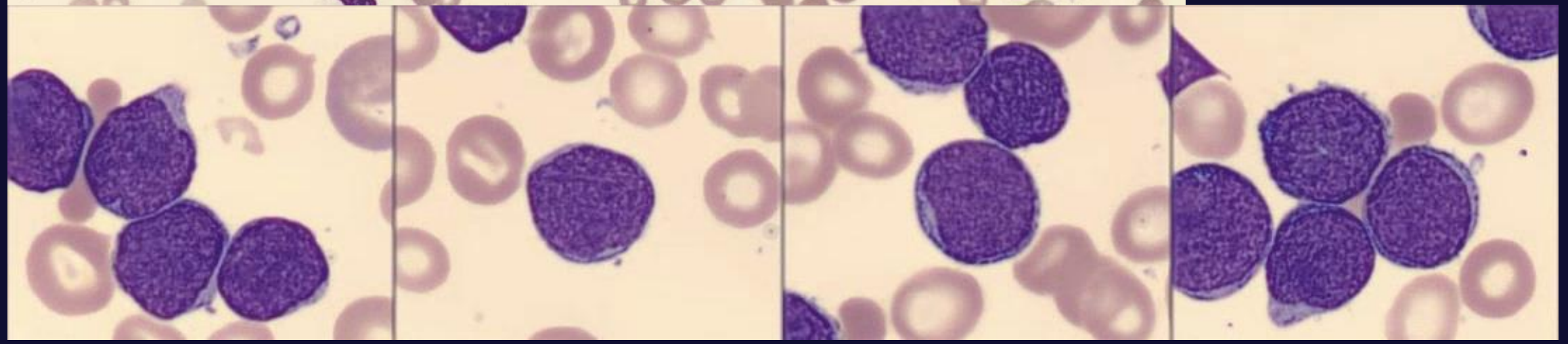
Presented with progressive dyspnea with low grade fever and bone pain

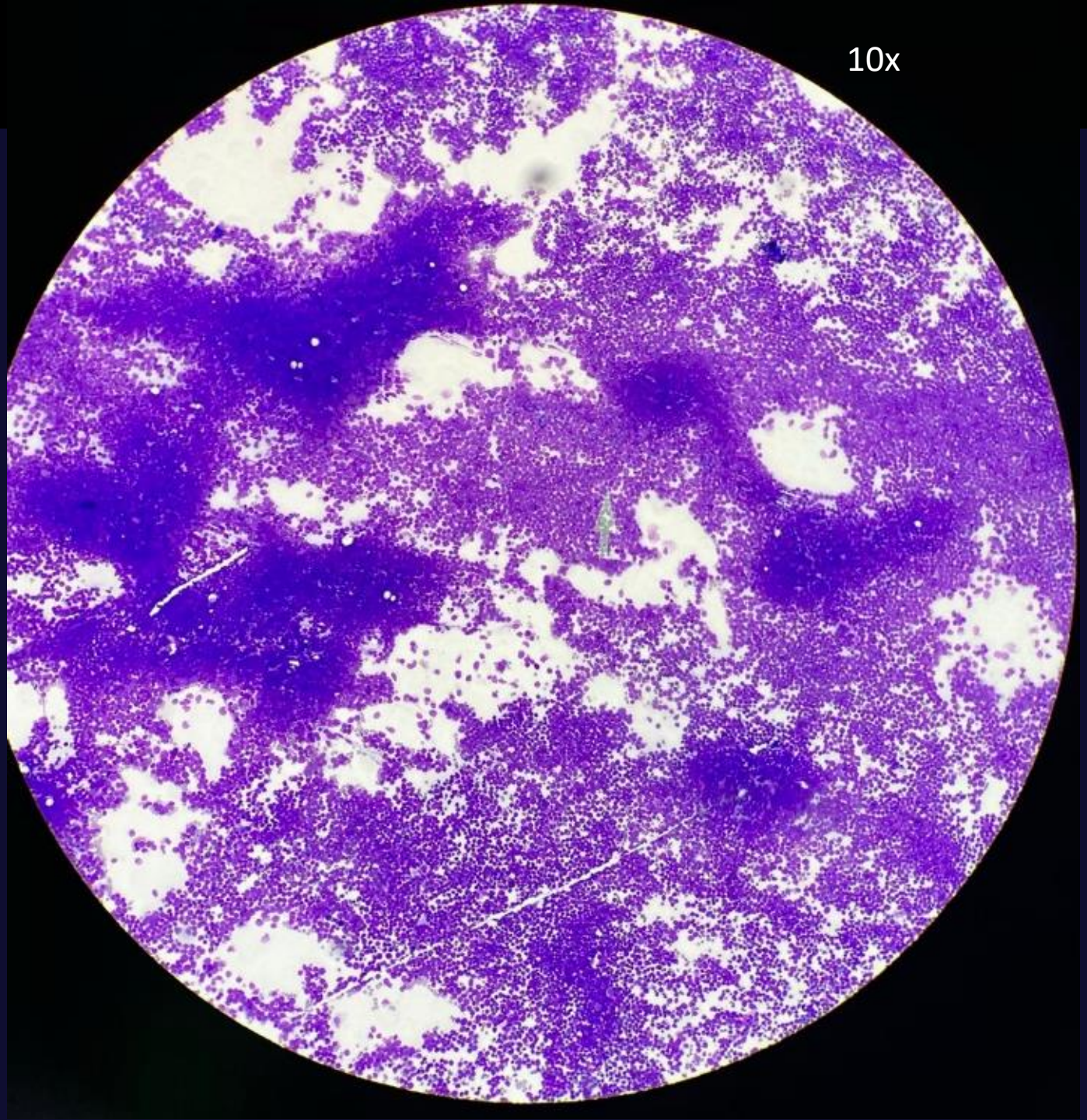


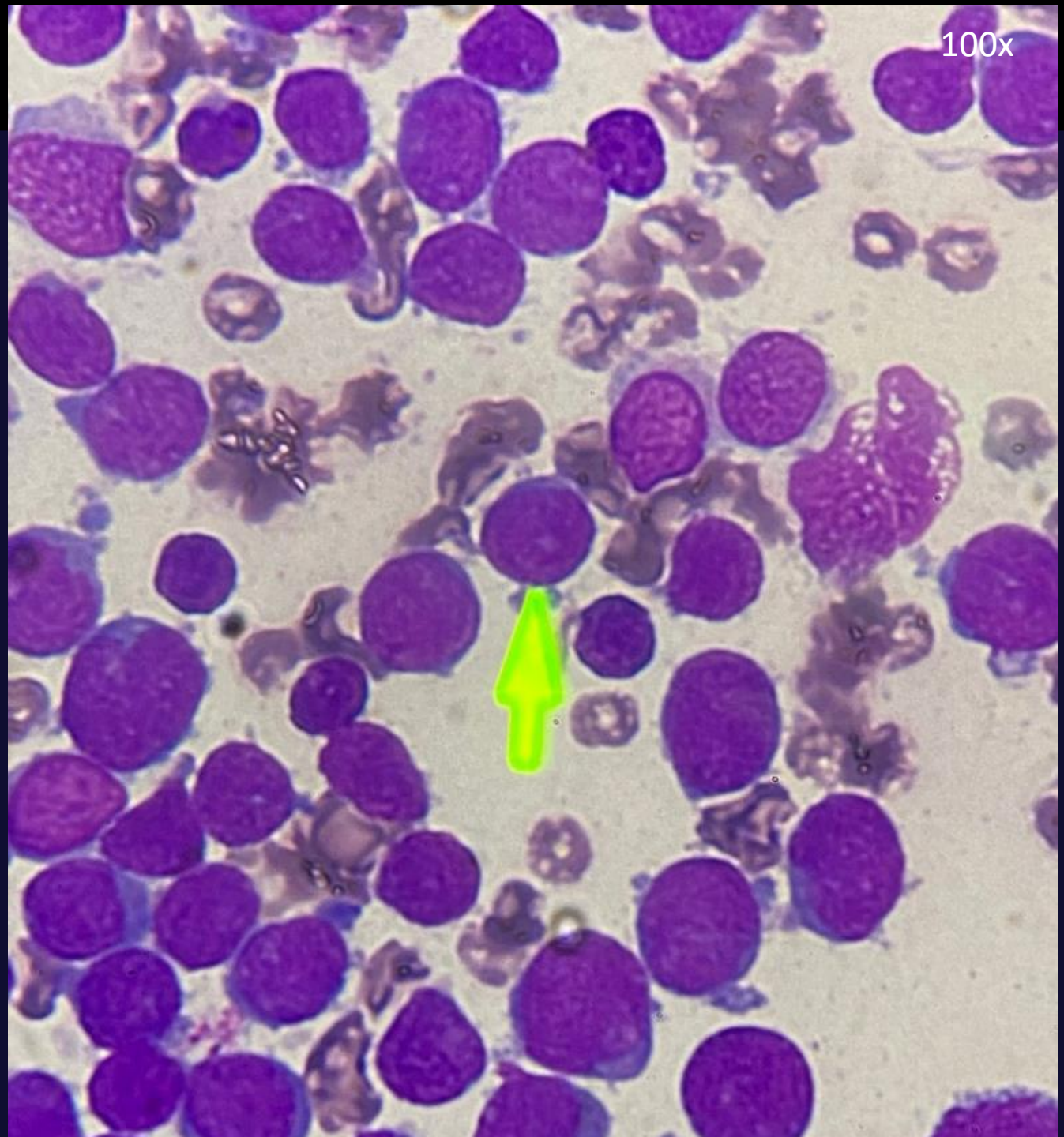
CBC / EDTA blood				
RBC	3.46	10^6/uL	L	4.70 - 6.20
HGB	9.1	g/dL	L	13.0 - 16.7
HCT	29.2	%	L	40.5 - 50.8
MCV	84.4	fL	-	80.0 - 97.8
MCH	26.3	pg	-	25.2 - 32.0
MCHC	31.2	g/dL	-	29.9 - 34.3
RDW	16.5	%	H	11.9 - 14.8
WBC	97.25	10^3/uL	H	4.60 - 10.60
PLT	31	10^3/uL	L	173 - 383
MPV	---	fL	-	8.7 - 12.5
Plt smear	Decreased		-	
Blast	89.0	%	-	
NE%	2.0	%	L	43.7 - 70.9
LY%	8.0	%	L	20.1 - 44.5
MO%	1.0	%	L	3.4 - 9.8



ALL







Satisfied marrow

Hypercellularity 3+

Decrease megakaryocyte 3+

Decrease myeloid 3+

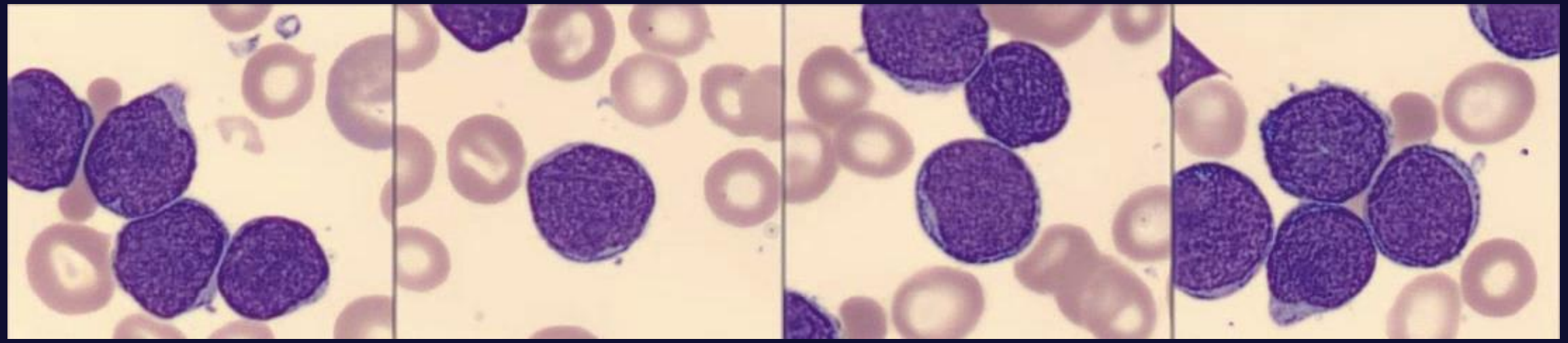
Decrease erythroid 3+

Diffuse infiltration of lymphoblast 90%

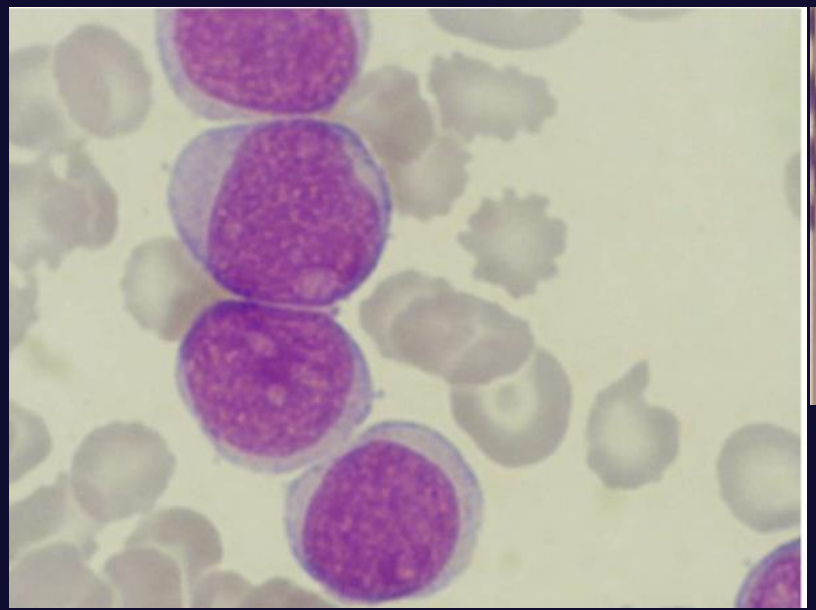
Imp: acute lymphoblastic leukemia

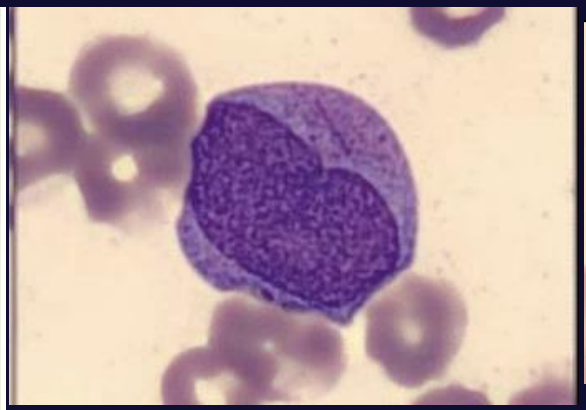
AML vs ALL

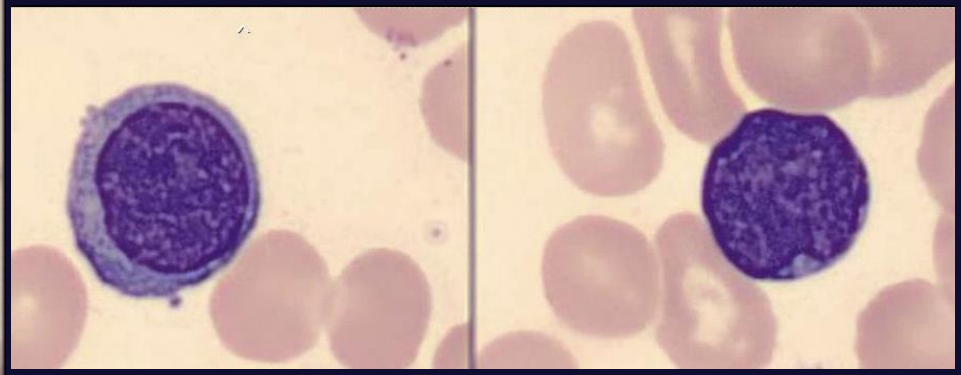
ALL



AML

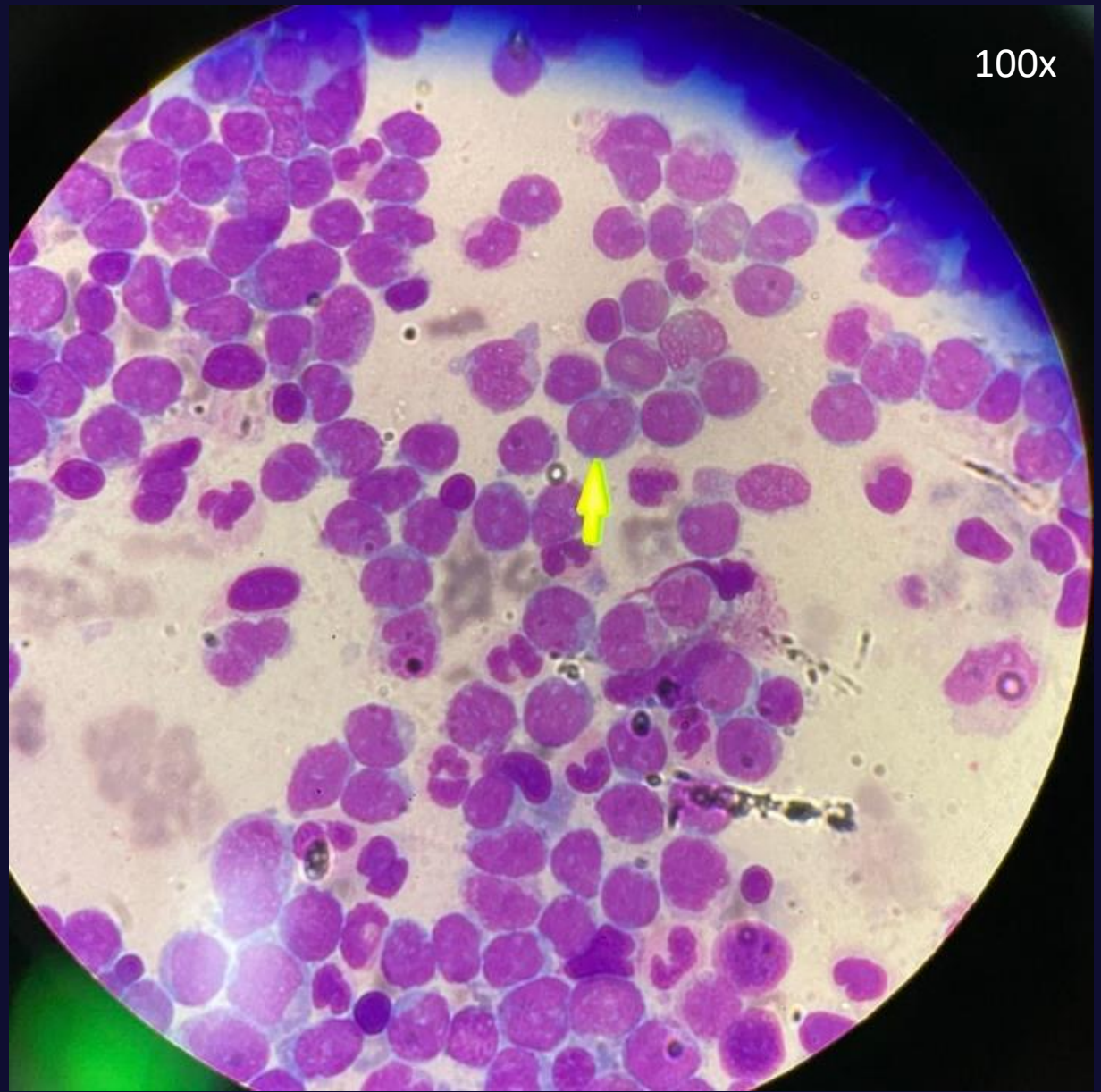




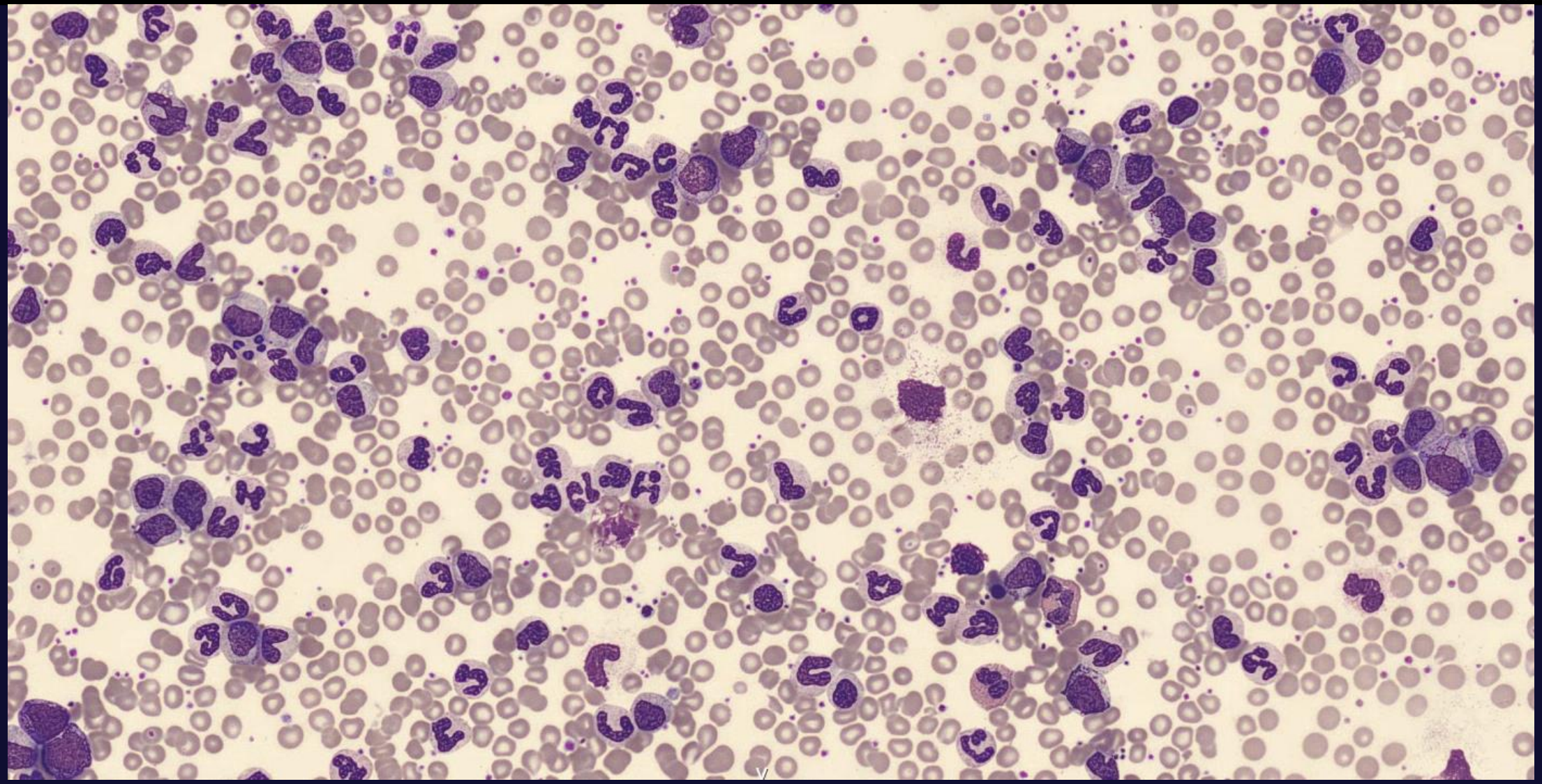


CLL

AML

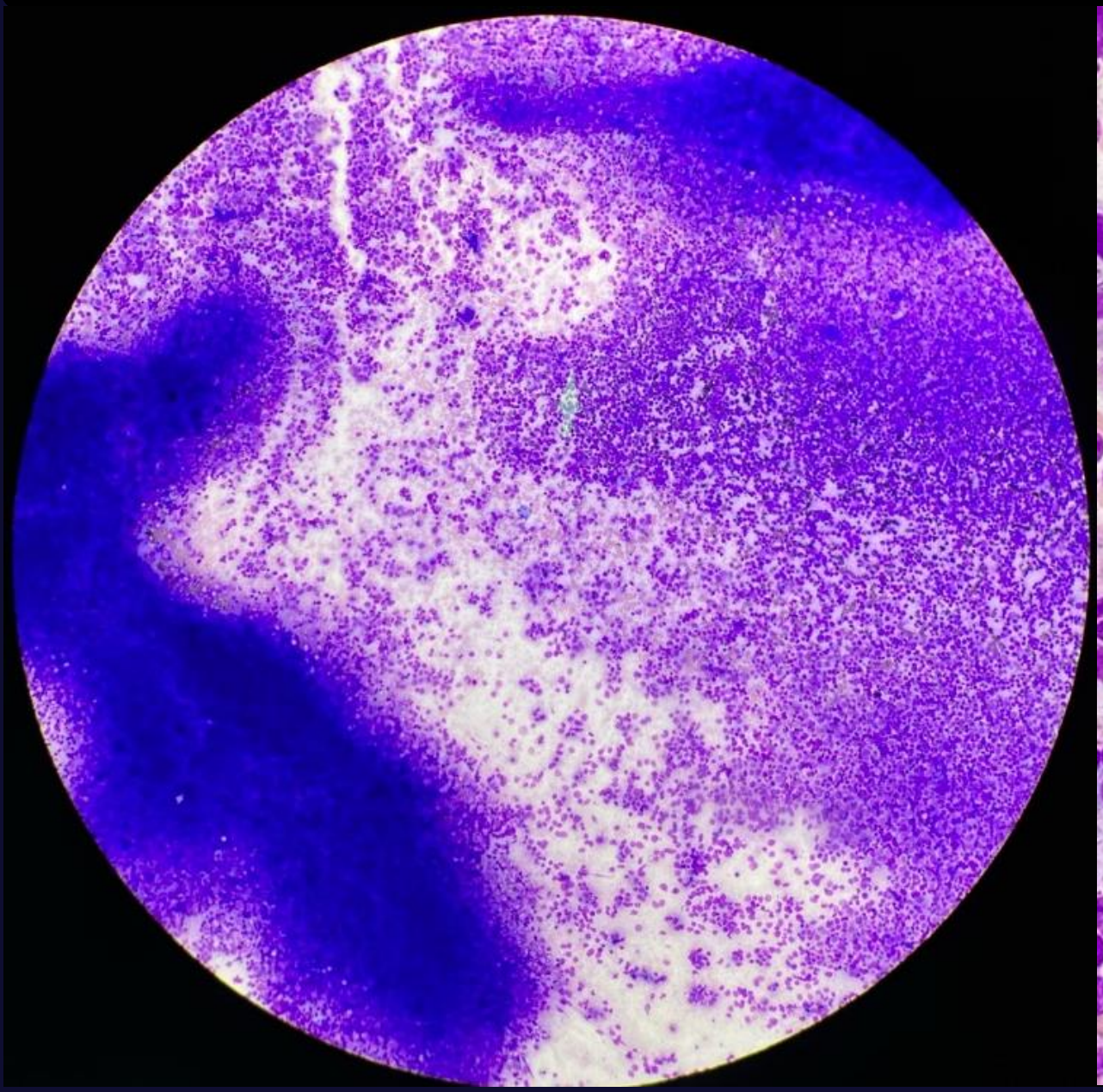


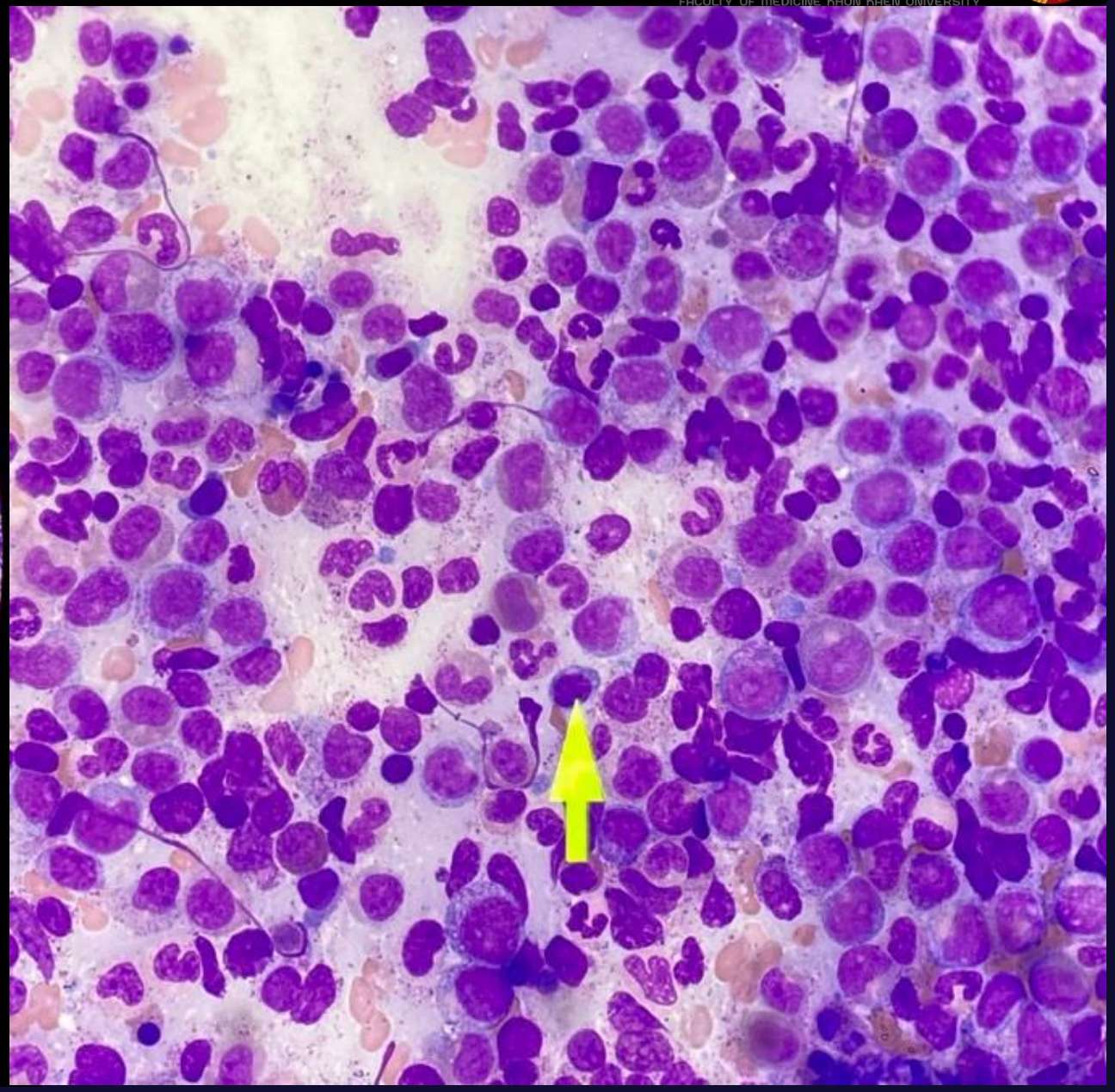
Blood Smear



Leukocytosis with multistage of myeloid series

Bone Marrow





Satisfied marrow

Hypercellularity 3+

Dwarf megakaryocyte, normal amount

M:E=20:1

Increase myeloid 3+

Normal erythroid

Blast 3%

Basophil 5%

Imp: CML chronic phase

Investigation

Chromosome or FISH for t(9;22)

PCR for BCR-ABL fusion gene

Phase of CML

Criteria	IBMTR	MDACC	ELN	WHO
ACCELERATED PHASE				
Blasts (PB or BM)	10–29%	15–29%	15–29%	10–19%
Blasts plus promyelocytes (PB or BM)	>20%	≥30% with blasts <30%	≥30% with blasts <30%	–
Basophils (PB)	≥20%	≥20%	≥20%	≥2
WBC	>100 × 10^9/L	>100 × 10^9/L	–	unres
Thrombocytopenia	<100 × 10^9/L unrelated to therapy	<100 × 10^9/L unrelated to therapy	<100 × 10^9/L unrelated to therapy	<100 unrelated
Thrombocytosis	>1,000 × 10^9/L unresponsive to tx	–	–	>1,000 × unresponsiv
Anemia	Hb<8 g/dL, unresponsive to tx	–	–	–
Splenomegaly	Unresponsive to tx	Unresponsive to tx	–	Unrespon
Cytogenetics	CE, on treatment	CE, on treatment	ACA/Ph+ major route, on treatment	ACA/Ph aryotype, or 3q26 any , or
Response to TKI (provisional criteria)	–	–	–	Fa CHR t or ical, cytoge cular indicat esistance to 2 ntial TKIs, or Occurrence of ≥2 mutations in BCR-ABL1 during TKI therapy
BLAST PHASE				
Blasts (PB or BM)	≥30%	≥30%	≥30%	≥20%
Other	Extramedullary blast proliferation (apart from spleen)	Extramedullary blast proliferation (apart from spleen)	Extramedullary blast proliferation (apart from spleen)	Extramedullary blast proliferation, or large foci or clusters of blasts in the BM biopsy

IBMTR, International Blood and Marrow Transplant Registry; MDACC, M.D. Anderson Cancer Center; ELN, European LeukemiaNet; WHO, World Health Organization; PB, peripheral blood; BM, bone marrow; CE, clonal evolution; ACA/Ph+, additional chromosome abnormalities in Philadelphia-positive cells; CHR, complete hematologic response.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Chronic Myeloid Leukemia

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Table of Contents
Discussion

DEFINITIONS OF ADVANCED PHASE CML[a]

Clinical trials in the TKI era have mostly utilized the modified MD Anderson Cancer Center (MDACC) criteria[1,2] or the International Bone Marrow Transplant Registry (IBMTR) criteria.[3] The use of the International Consensus Classification (ICC)[4] or the World Health Organization (WHO) criteria[5] for the diagnosis of AP-CML and BP-CML is not recommended.

AP-CML[b]	BP-CML
Modified MDACC Criteria[1,2] • Peripheral blood myeloblasts ≥15% and <30% • Peripheral blood myeloblasts and promyelocytes combined ≥30% • Peripheral blood basophils ≥20% • Platelet count ≤100 x 10^9/L unrelated to therapy • Additional clonal cytogenetic abnormalities in Ph+ cells[c]	**IBMTR criteria[3]** • ≥30% blasts in the blood, marrow, or both • Extramedullary infiltrates of leukemic cells

Management

Tyrosine kinase inhibitor

- Imatinib / Dasatinib / Nilotinib → Failx3 → Ponatinib

T315I mutation

พยากรณ์โรคดีมากถ้ากินยาสม่ำเสมอ

ในระยะยาวถ้าโรคตอบสนองได้ดีมากและอยู่ในที่ที่ตรวจเลือดแบบละเอียดได้ อาจจะพิจารณาหยุดยาได้ถ้าต้องการ

Discontinuation of TKI

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Chronic Myeloid Leukemia

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Discussion

DISCONTINUATION OF TKI THERAPY

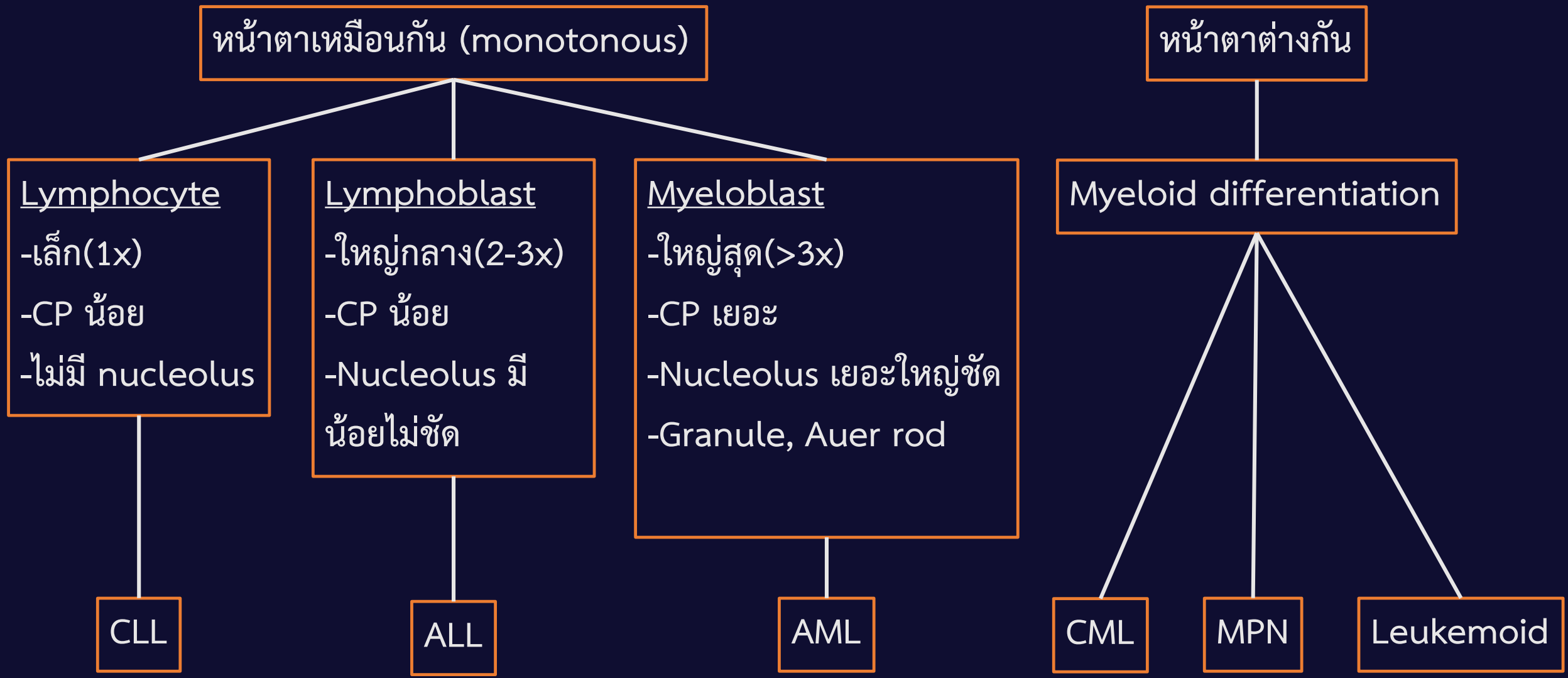
General Considerations

- Discontinuation of TKI therapy appears to be safe in select patients with CML.
- Consult with a CML specialist to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
- Discontinuation of TKI therapy should only be performed in patients who give consent after a thorough discussion of the potential risks and benefits.
- Consultation with an NCCN Panel Member or center of expertise is recommended in the following circumstances:
  - Any significant adverse event is believed to be related to treatment discontinuation.
  - There is progression to AP-CML or BP-CML at any time.
  - MMR is not regained after 3 months following treatment reinitiation.
- Outside of a clinical trial, discontinuation of TKI therapy should be considered only if ***all*** of the criteria included in the list below are met.

Criteria for TKI Discontinuation

- Age ≥18 years.
- CP-CML. No prior history of AP-CML or BP-CML.
- On approved TKI therapy for at least 3 years.[1,2]
- Prior evidence of quantifiable *BCR::ABL1* transcript.
- Stable molecular response (MR4; *BCR::ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[2]
- Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR::ABL1* ≤0.0032% IS) and that provides results within 2 weeks.
- Molecular monitoring every 1–2 months for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; *BCR::ABL1* ≤0.1% IS).
- Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. If MMR is not achieved after 3 months of TKI resumption, *BCR::ABL1* kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.

Approach to Leukocytosis by PBS



Case 7

Male 58-year-old

Hematoma at left flank 15x15 cm. for 5 days

▼ PT/INR				
PT	***11.7***	sec	9.2 - 12.0	-
INR	***1.17***			-
▼ aPTT				
aPTT	***>120***	sec	24.5 - 36.8	-
APTT Ratio	***>3.93***			-

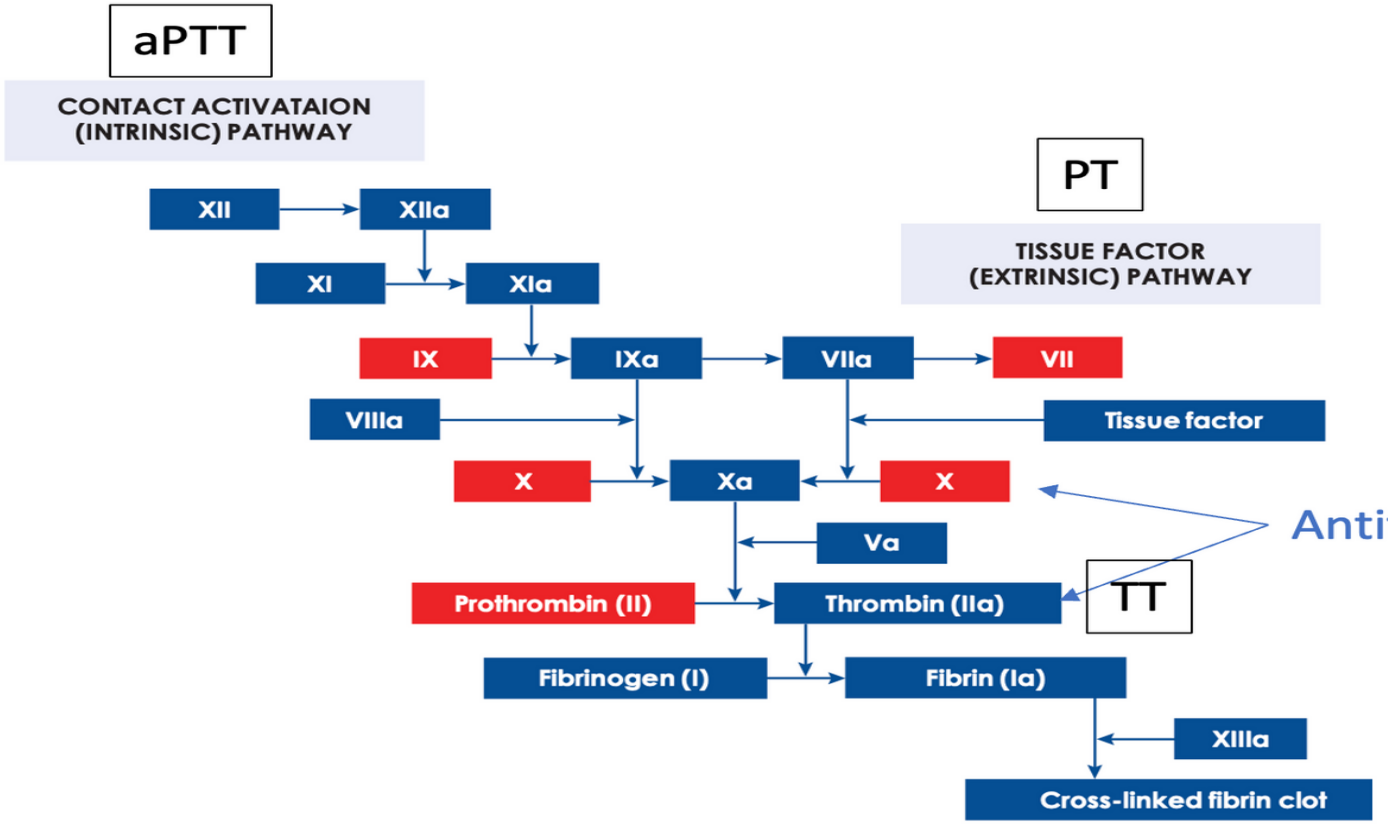
▼ Mixing test				
PT 0hr	***11.7***	sec	RNF	-
APTT 0hr	***34.4***	sec	RNF	-
PT 2hr	***12.7***	sec	RNF	-
APTT 2hr	***88.5***	sec	RNF	-

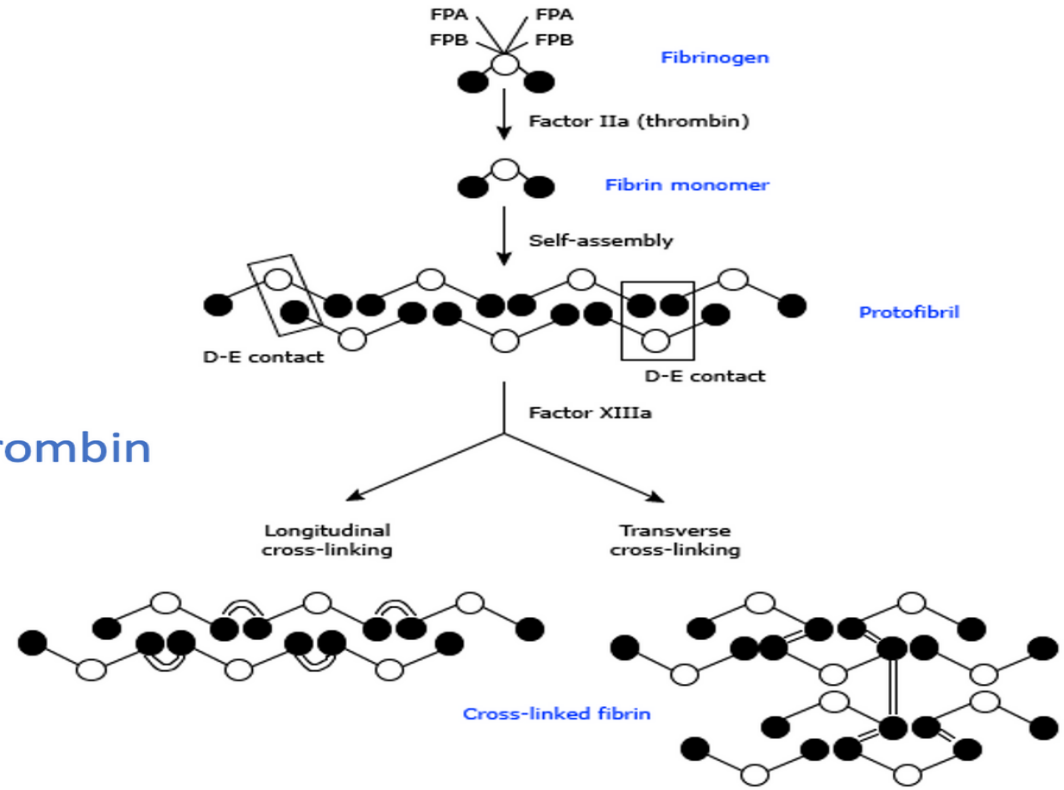
Secondary Hemostasis

คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น
FACULTY OF MEDICINE KHON KAEN UNIVERSITY

Waterfall cascade "describe coagulogram"

- Intrinsic: factor XII, XI, IX, VIII
- Extrinsic: factor VII, TF
- Common: factor X, V, II, I
- no effect on coagulogram:
  - Factor XIII





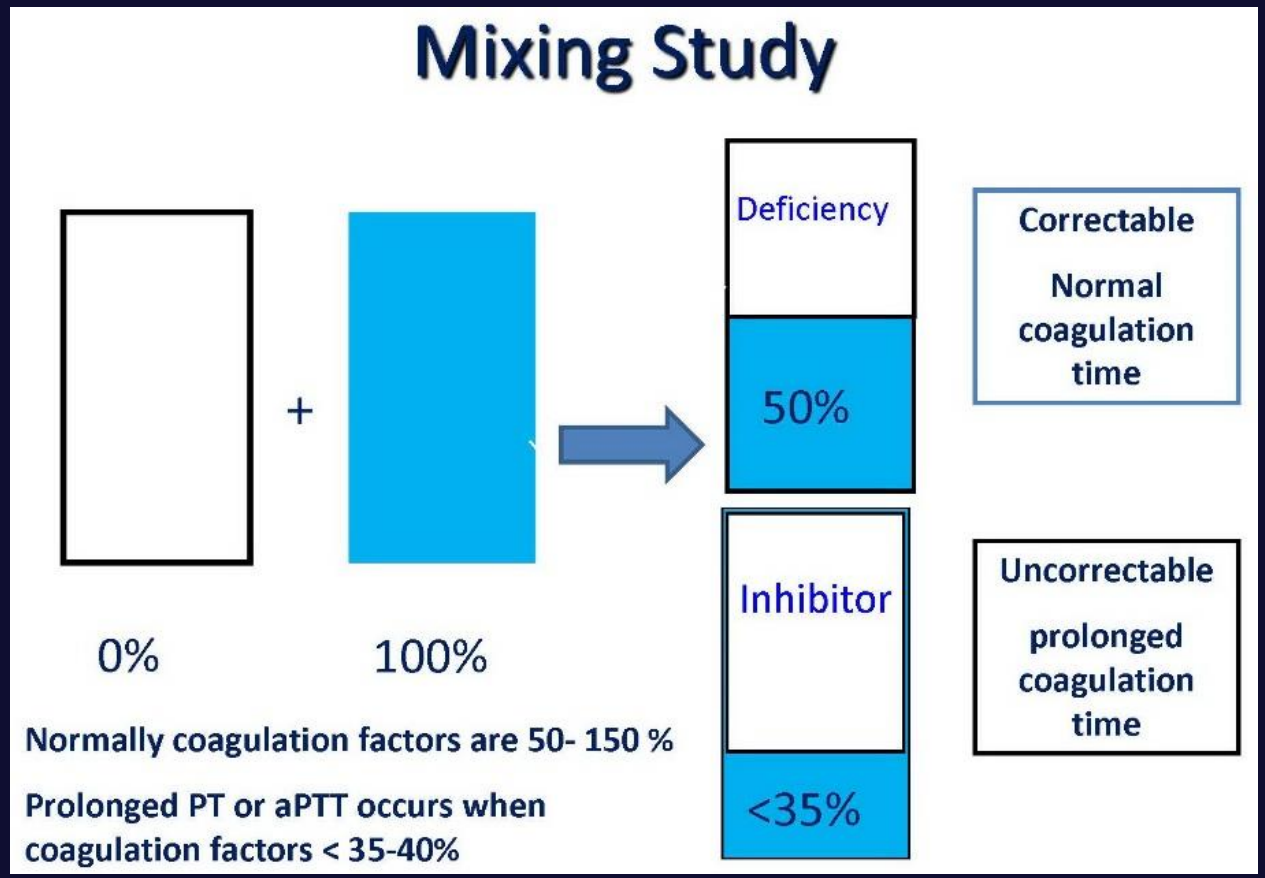
Mixing Test (PT or aPTT)

Uncorrectable

- at 0 and 2 hr : antiphospholipid syndrome
- at 2 hr “time and temperature dependent” : Factor VIII inhibitor

Correctable

- Factor deficiency



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Thank you

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