NHS North Midlands and Cheshire Pathology Service

University Hospitals of North Midlands NHS Trust

SUPERHERO OR VILLAIN

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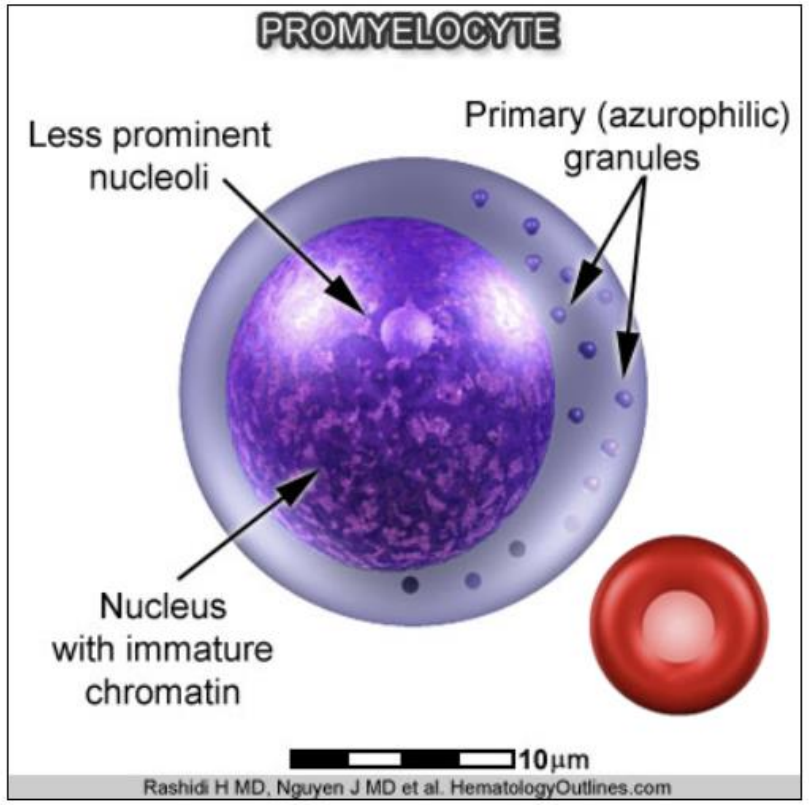
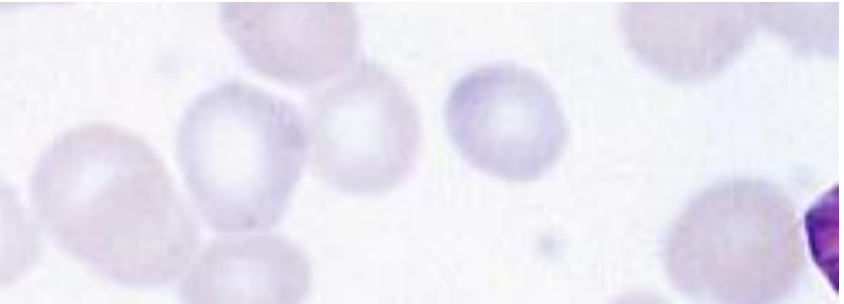


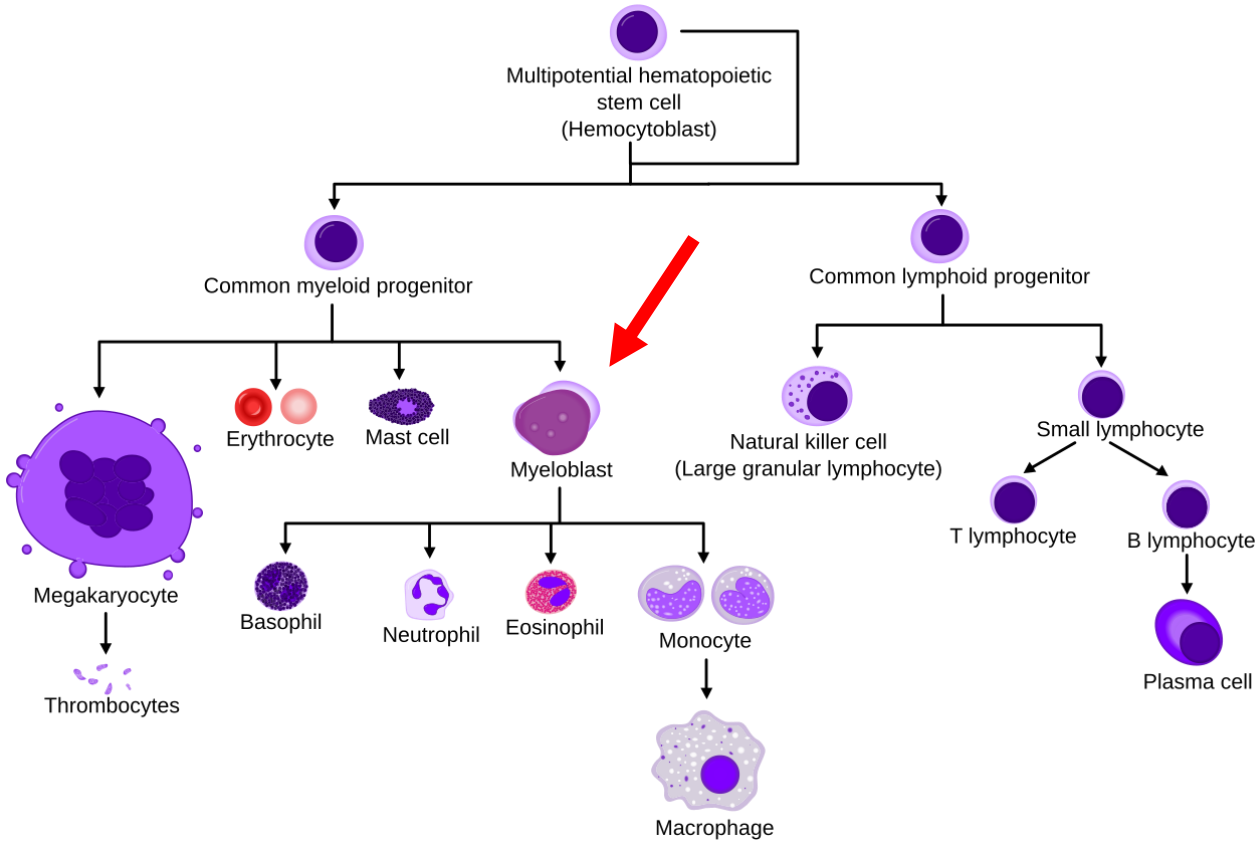


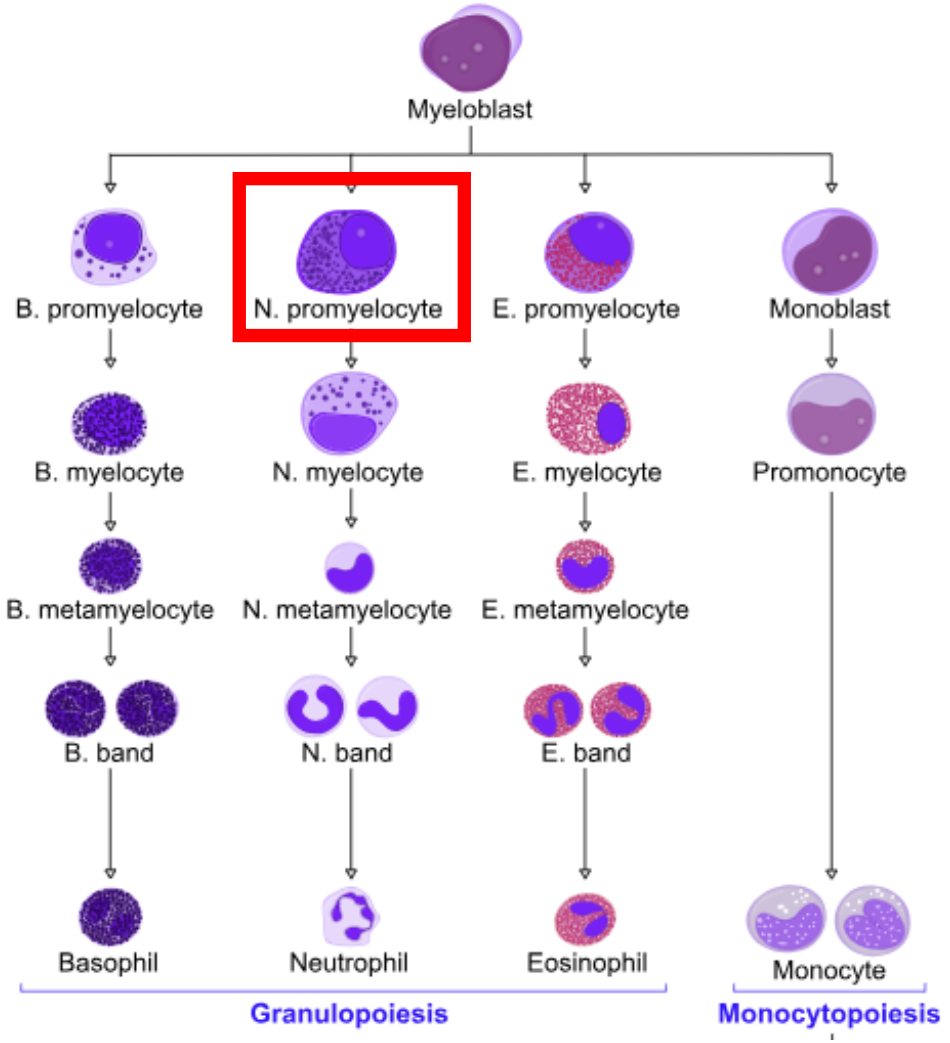
SUPERHERO OR VILLAIN?

- Promyelocytes are larger than myeloblasts and measure approximately 12–20 microns in diameter
- The nucleus of a promyelocyte is approximately the same size as a myeloblast but their cytoplasm is much more abundant
- The cytoplasm is basophilic and contains primary red/purple granules
- A Golgi zone may be visible as a paranuclear hof or clearing
- Promyelocytes have less prominent nucleoli than myeloblasts but they may be visible
- The nuclear chromatin is often described as finely dispersed but it is slightly coarser than a myeloblast
- Promyelocytes comprise approximately 2% of nucleated cells in the bone marrow and do not circulate in peripheral blood under normal conditions

HematologyOutlines – Atlas RBC size comparison

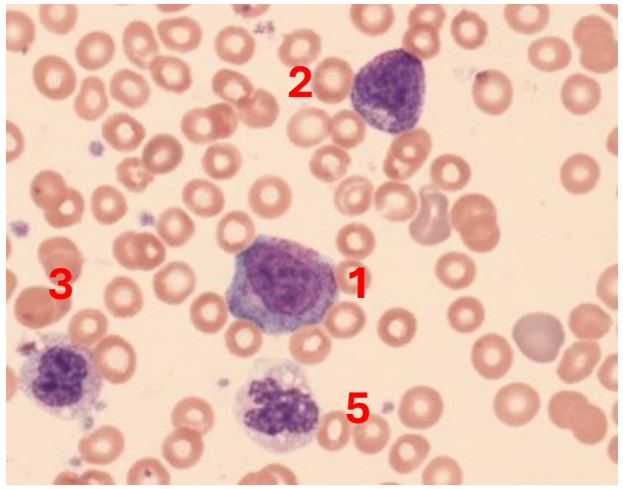
GRANULOPOIESIS





- Image: Hematopoiesis (human) diagram.png by A. Rad, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=7351905

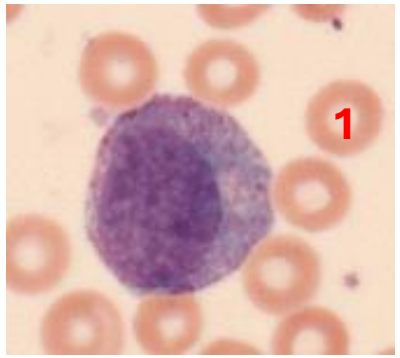
SUPERHERO

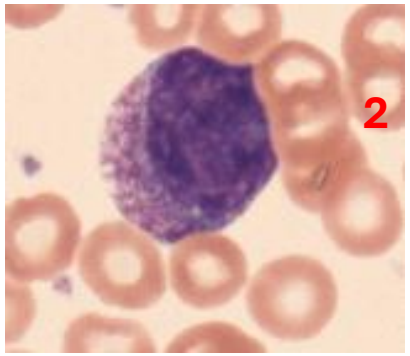


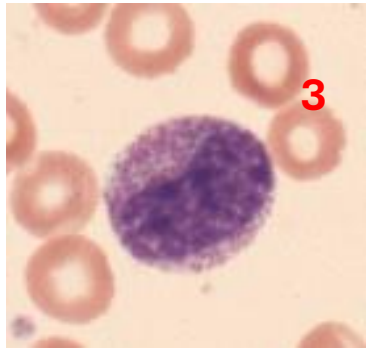
Key for all images:

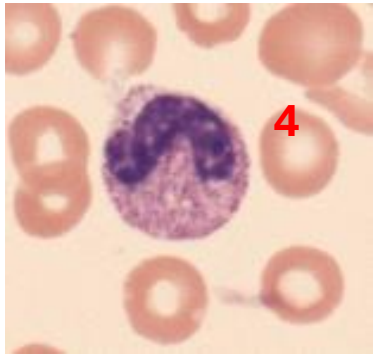
1. Promyelocyte
2. Myelocyte
3. Metamyelocyte
4. Band Form Neutrophil
5. Neutrophil
6. Toxic Vacuolated Neutrophil

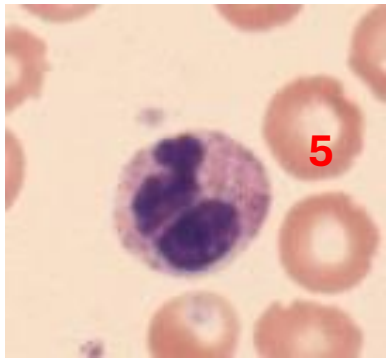
- Promyelocytes play an essential role in haematopoiesis by serving as an intermediate in the differentiation pathway leading to mature granulocytes
- Granulocytes are a vital part of the innate immune system

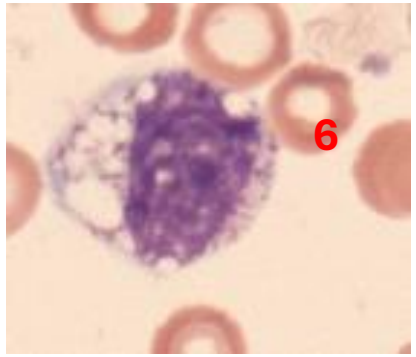












VILLAIN

Patient 1 – 69yo male, unwell, GP

14. Tests	Result	Units	Flags and Ref. Ranges	Status
Haemoglobin	79	g/L	L (120 - 170)	R
White Cell Count	1.9	10*9/L	L (4.0 - 11.0)	R
Platelets	22	10*9/L	L (150 - 450)	R
Red Cell Count	2.27	10*12/L	L (4.30 - 5.70)	R
Haematocrit	0.210		L (0.37 - 0.51)	R
Mean Cell Volume	92.3	fL	(80 - 100)	R
Mean Cell Haemoglobin	35.0	pg	H (26.5 - 31.5)	R
Mean Cell Hb Concentration	379	g/L	H (300 - 350)	R
Mean Platelet Volume	9.9	fl		R
Red cell distribution width	17.8			R
Platelet distribution width	63.6			R
% Hypochromic Red Cell	0.9	%	(<5.0)	R
Neut (abs no)	0.90	10*9/L	L (2.0 - 7.5)	R
Lymph (abs no)	0.70	10*9/L	L (1.10 - 3.60)	R

14. Tests	Result	Units	Flags and Ref. Ranges	Status
>Mono (abs no)	0.00	10*9/L	L (0.20 - 0.80)	R
Eos (abs no)	0.20	10*9/L	(0.04 - 0.40)	R
Bas (abs no)	0.00	10*9/L	(0.0 - 0.10)	R
LUCs (abs no)	0.00	10*9/L	(0.00 - 0.44)	R
Neutrophils (%)	49	%	(40 - 75)	R
Lymphocytes (%)	36	%		R
Monocytes (%)	1	%	L (2 - 10)	R
Eosinophils (%)	10	%	H (1 - 6)	R
Basophils (%)	2	%	H (0 - 1)	R
Large unstained cells (%)	3	%		R
Blast Flag	+++			R
Atypical Lymph Flag				
Myelo-peroxidase Def. Flag				
Blood film	Blood film examined			R

INR	1.2
D-dimer	4428 ng/mL
Fibrinogen	2.65 g/L

Patient 2 – 33yo male, bruising, A&E

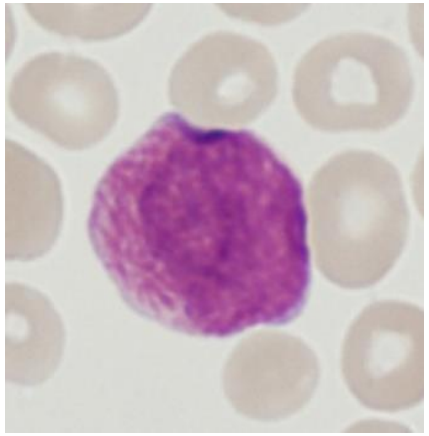
Haemoglobin	111	g/L	L (120 - 170)	R
White Cell Count	54.3	10*9/L	H (4.0 - 11.0)	R
Platelets	34	10*9/L	L (150 - 450)	R
Red Cell Count	3.27	10*12/L	L (4.30 - 5.70)	R
Haematocrit	0.299		L (0.37 - 0.51)	R
Mean Cell Volume	91.6	fL	(80 - 100)	R
Mean Cell Haemoglobin	34.0	pg	H (26.5 - 31.5)	R
Mean Cell Hb Concentration	371	g/L	H (300 - 350)	R
Mean Platelet Volume	9.9	fl		R

14. Tests	Result	Units	Flags and Ref. Ranges	Status
>Red cell distribution width	16.8			R
Platelet distribution width	81.1			R
% Hypochromic Red Cell	0.6	%	(<5.0)	R
Neut (abs no)	2.17	10*9/L	(2.0 - 7.5)	R
Lymph (abs no)	2.17	10*9/L	(1.10 - 3.60)	R
Mono (abs no)	0	10*9/L	L (0.20 - 0.80)	R
Eos (abs no)	0	10*9/L	L (0.04 - 0.40)	R
Bas (abs no)	0	10*9/L	(0.0 - 0.10)	R
LUCs (abs no)	0	10*9/L	(0.00 - 0.44)	R
>Large unstained cells (%)	0	%		R
Blast Flag	+++			R
Atypical Lymph Flag				
Myelo-peroxidase Def. Flag				
Urgent blood film	Blood film examined			R
Atyp Lymph (abs no)	0.00			R
Metamye (abs no)	0.00	10*9/L		R
Myelo (abs no)	0.00	10*9/L		R
Promye (abs no)	47.78	10*9/L		R
Blast (abs no)	2.17	10*9/L		R
Atypical Lymphocytes (%)	0	%		R
Metamyelocytes (%)	0	%		R
Myelocytes (%)	0	%		R
Promyelocytes (%)	88	%		R

INR	1.5
D-dimer	32078 ng/mL
Fibrinogen	1.02 g/L

APL - MORPHOLOGY

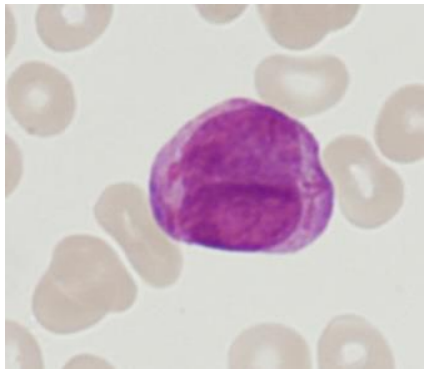
- Nuclear size and shape in the abnormal promyelocytes of hypergranular APL are irregular and greatly variable; they are often kidney shaped or bilobed



- Cytoplasm is marked by densely-packed large granules, staining bright pink, red or purple in Romanowsky stains

- Cytoplasmic granules may be so large and/or numerous that they totally obscure the nuclear cytoplasmic margin. In some cells, the cytoplasm is filled with fine dust-like granules

- Characteristic cells containing bundles of Auer rods (“faggot cells”) randomly distributed in the cytoplasm are present in most cases

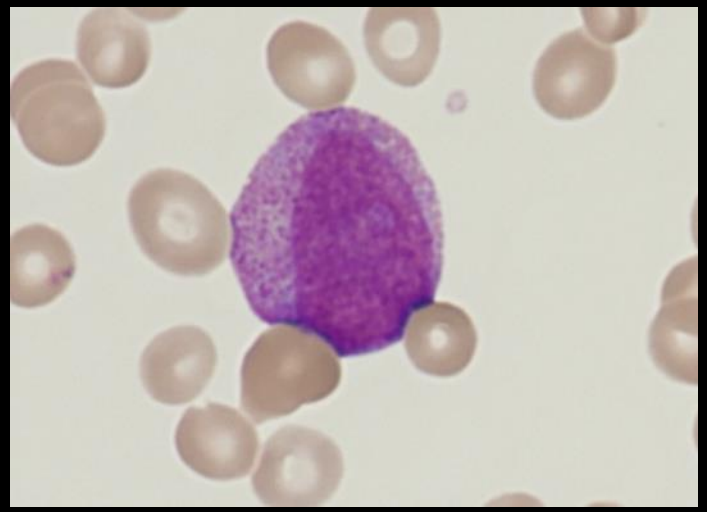


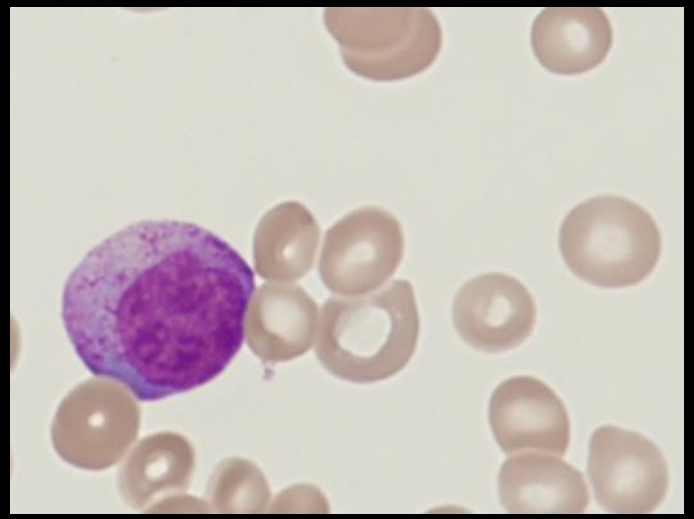
- Myeloblasts with single Auer rods may also be observed

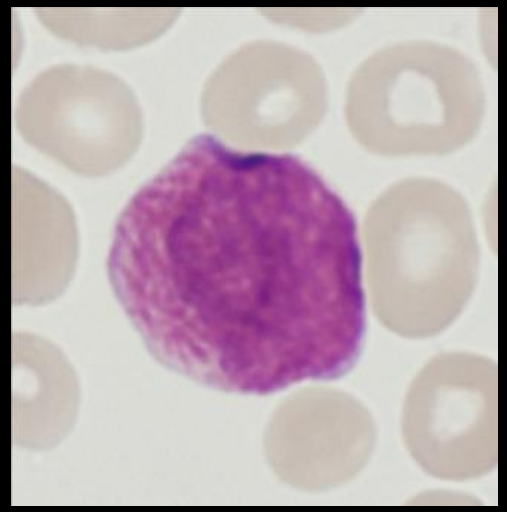
- Auer rods in hypergranular APL are usually larger than in other types of AML

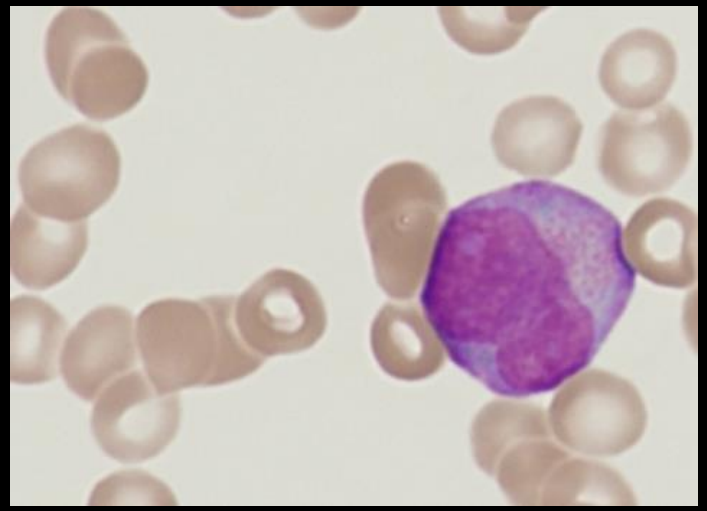
PROMYELOCYTE MORPHOLOGY PATIENT 1

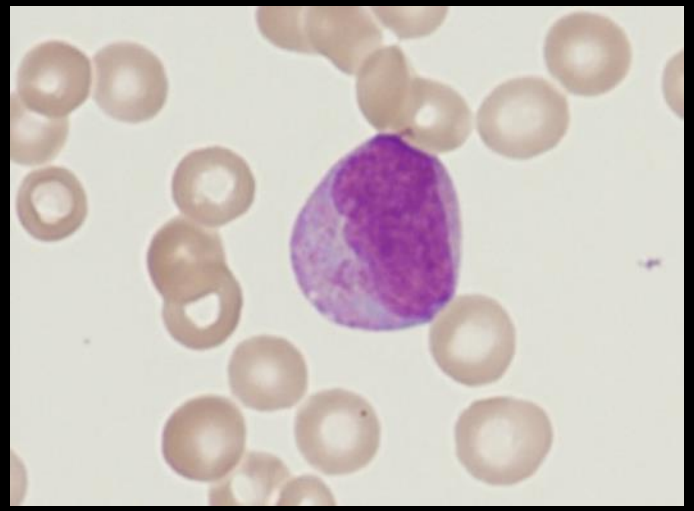
HYPERGRANULAR





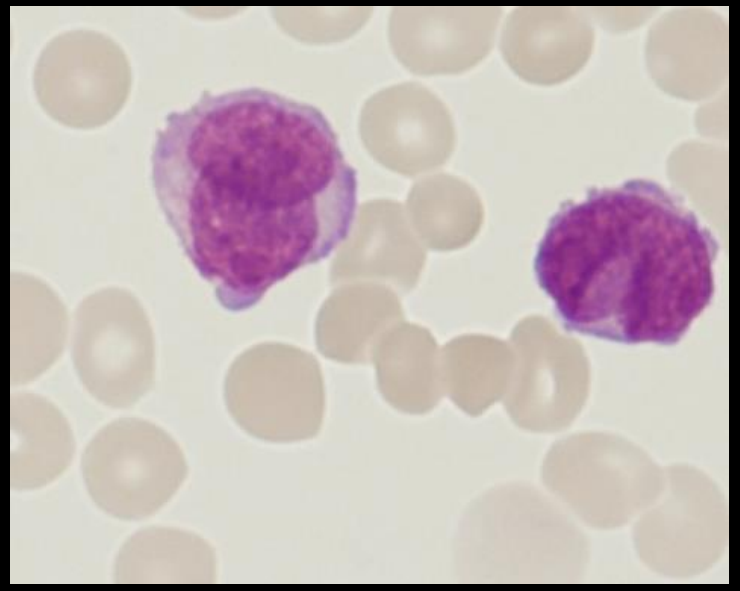


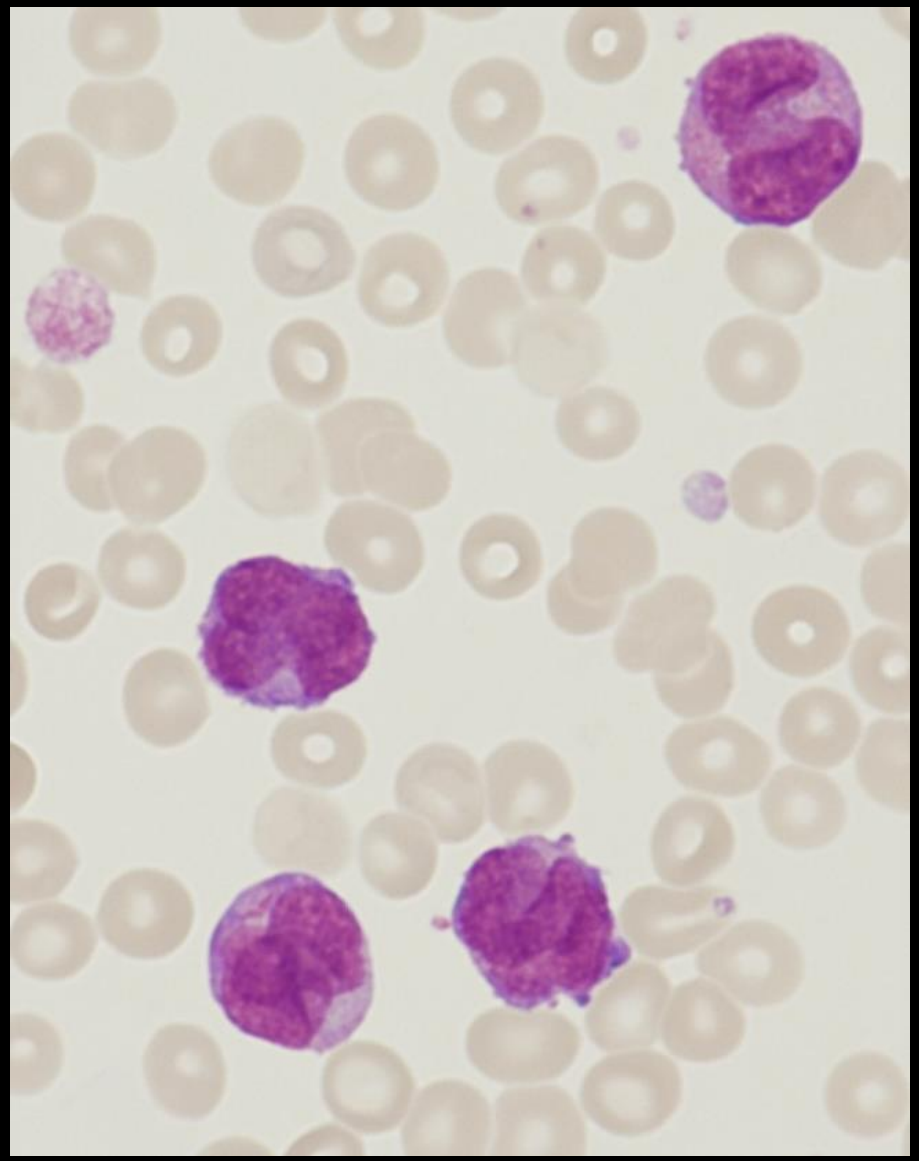


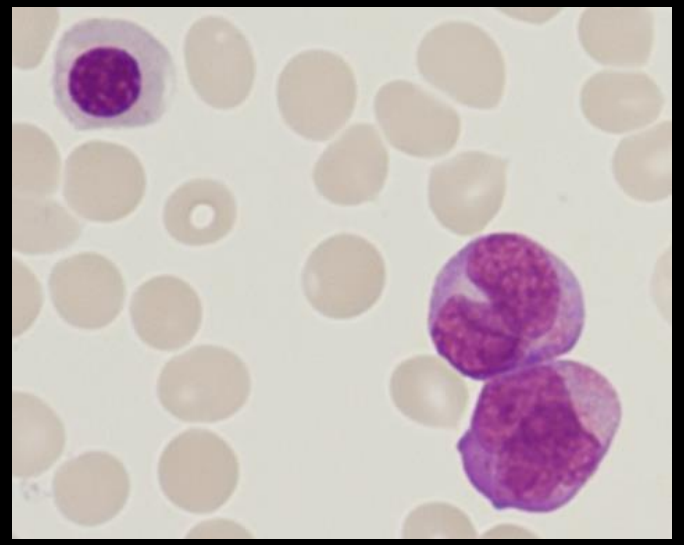


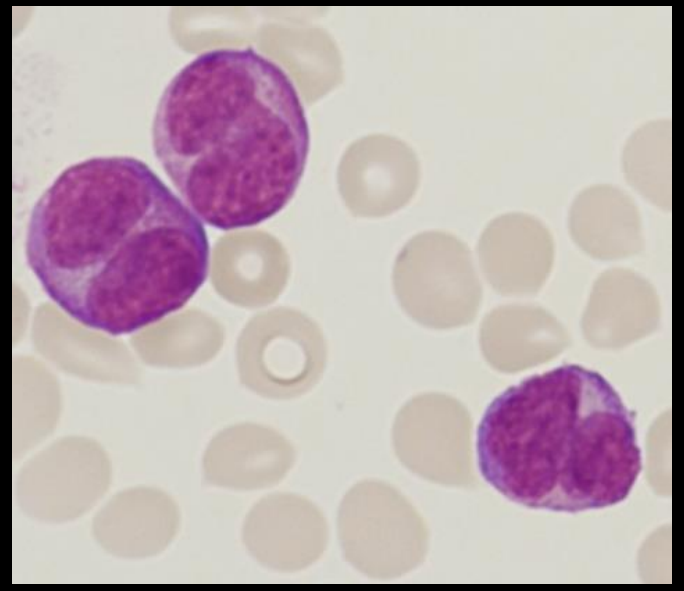
PROMYELOCYTE MORPHOLOGY PATIENT 2

MICROGRANULAR









GENETICS

PATIENT 1

Karyotype:

10 metaphase cells examined by G-band chromosome analysis

45, X-Y, t(15;17)(q24;q21), add 15 (q25), -22 (9)
46, XY (1)

PML::RARA gene rearrangement

48/50 (96%) cells had an abnormal signal pattern consistent with a *PML::RARA* gene rearrangement

Classified as Acute Promyelocytic Leukaemia with *PML::RARA* (WHO 2022)

PATIENT 2

Karyotype:
20 metaphase cells examined by G-band chromosome analysis
46,XY (20)

No evidence of a *PML::RARA* rearrangement
No evidence of a RARA gene rearrangement (Interphase FISH)

21bp and 45bp FLT3-ITDs identified
No evidence of insertion/duplication variant within the NPM1 gene
(fragment analysis)

Positive for a *PML::RARA* fusion by nested RT-PCR and by RQ-PCR

Consistent with a cytogenetically cryptic *PML::RARA* rearrangement

Classified as Acute Promyelocytic Leukaemia with *PML::RARA* (WHO 2022)

COAGULOPATHY

Lab Results

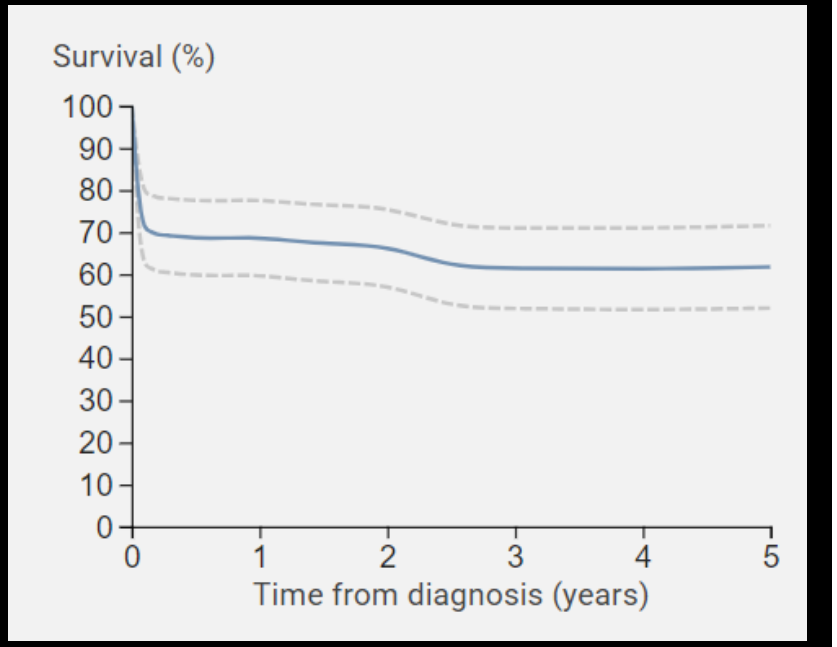
- Thrombocytopenia (<40 x10^9/L in 25%)
- Prolonged PT/APTT
- Increased D Dimer / Low fibrinogen
- Protein C, S and antithrombin not usually decreased (in contrast to DIC)
- Microvascular thrombosis uncommon
- Low platelets not solely consumptive
- Physiological anticoagulant levels preserved
- Lower fibrinogen and factor V
- D dimers higher

SUGGESTS PRIMARY DRIVER IS INCREASED FIBRINOLYTIC ACTIVTY

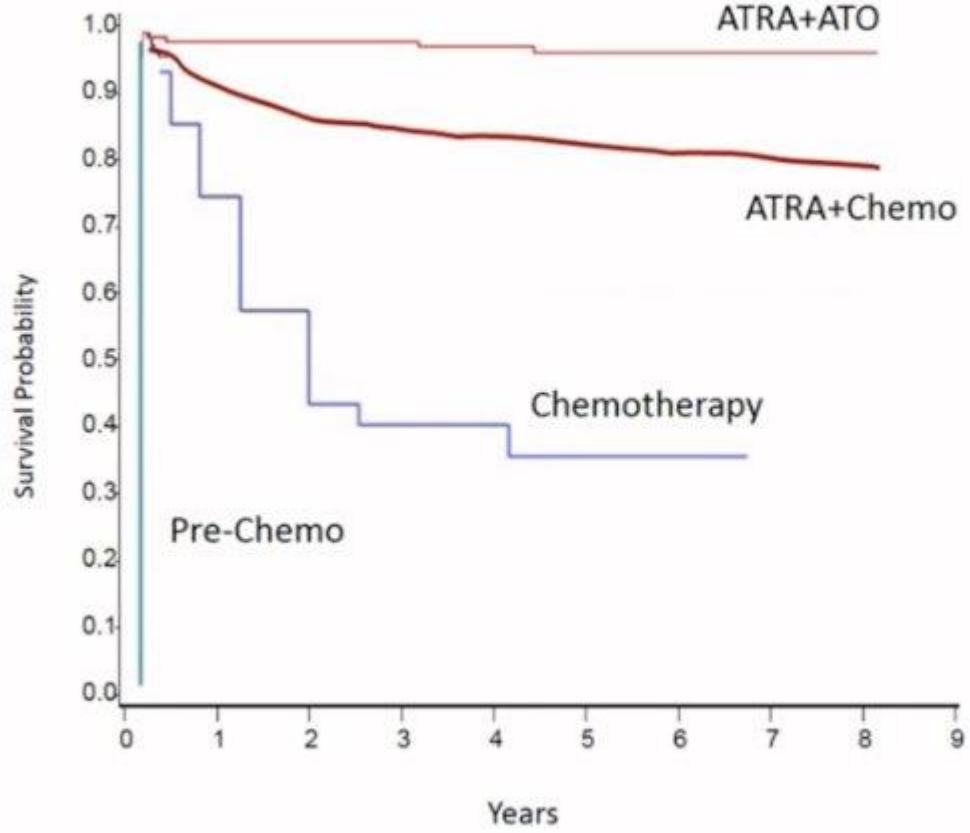
Risk Factors for Bleeding

- WCC >10 x10^9/L
- Fibrinogen <1.0 g/L
- PS <2
- High creatinine
- Platelets NOT predictive

SUPERHERO OR VILLAIN?



APL: From Highly Fatal to Highly Curable



ATRA: All Trans Retinoic Acid; ATO: Arsenic Trioxide

REFERENCES

1. Li W. The 5th Edition of the World Health Organization Classification of Hematolymphoid Tumors. In: Li W. editor. Leukemia. Brisbane (AU): Exon Publications. Online first 15 Sep 2022
2. Khoury, J.D., Solary, E., Abla, O. et al. The 5th Edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukaemia (2022) 36: 1703-1719
3. Alaggio R et al. The 5th Edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukaemia (2022) 36: 1720-1748
4. Arber, D. A. et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood 2022; 140 (11): 1200-1228
5. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. Blood. 2022;140 (11): 1229–1253
6. www.hmrn.org Promyelocyte Factsheet
7. Pei R, Si T, Lu Y, Zhang P, Liu X, Ye P. Clinical features and prognostic analysis of high-risk acute promyelocytic leukemia patients. Zhonghua xue ye xue za zhi= Zhonghua xueyexue zazhi. 2016;37(5):360–365. doi: 10.3760/cma.j.issn.0253-2727.2016.05.002.
8. Kwaan HC. editor The unique hemostatic dysfunction in acute promyelocytic leukemia. Seminars in thrombosis and hemostasis. Thieme Medical Publishers; 2014