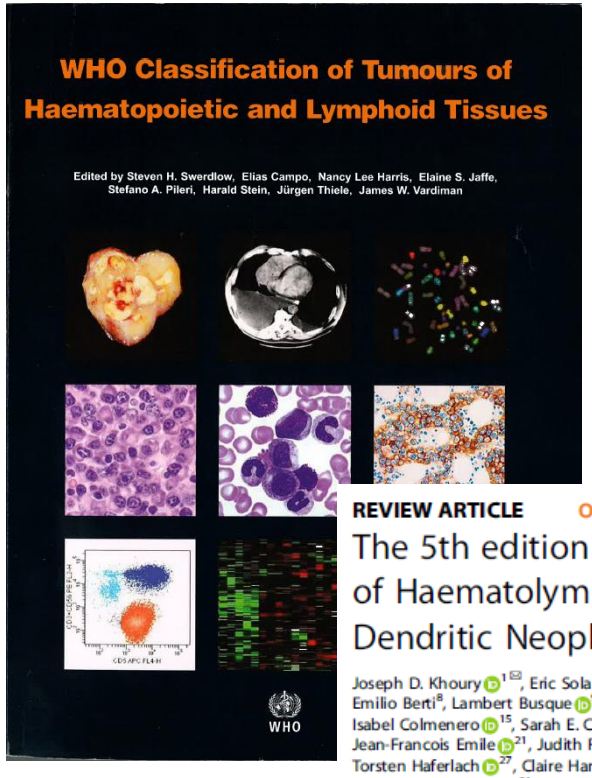
Diagnose en classificatie van acute myeloide leukemie

Basiscursus 2024 M.J. Wondergem

Disclosure belangen spreker

(potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	•niet relevant • •



THE UPDATED WHO CLASSIFICATION OF HEM

The 2016 revision to the World Health myeloid neoplasms and acute leukemia

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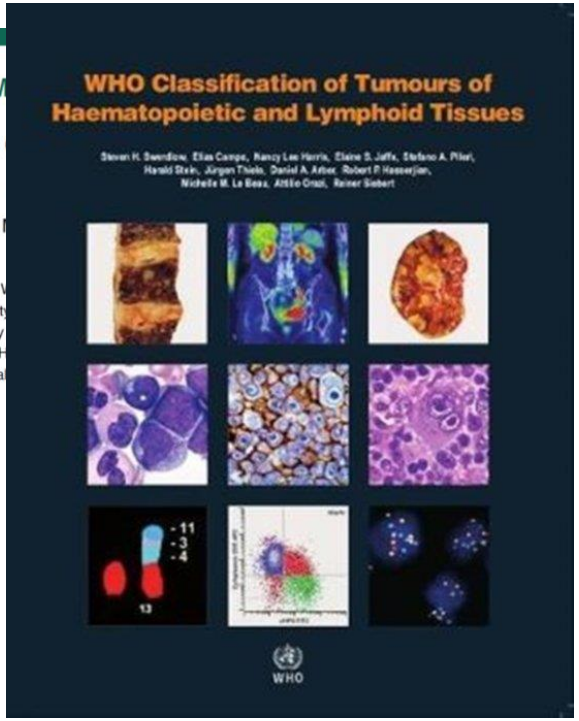


REVIEW ARTICLE OPEN

Check for updates

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury[1], Eric Solary[2], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52]

The upcoming 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours is part of an effort to hierarchically catalogue human cancers arising in various organ systems within a single relational database. This paper summarizes the new WHO classification scheme for myeloid and histiocytic/dendritic neoplasms and provides an overview of the principles and rationale underpinning changes from the prior edition. The definition and diagnosis of disease types continues to be based on multiple clinicopathologic parameters, but with refinement of diagnostic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers. While a genetic basis for defining diseases is sought where possible, the classification strives to keep practical worldwide applicability in perspective. The result is an enhanced, contemporary, evidence-based classification of

En nu:

Maar ook…
International Consensus Classification

Grote lijnen hetzelfde, kleine verschillen

Diagnostische methoden

morfologie
- May-Grunwald Giemsa kleuring

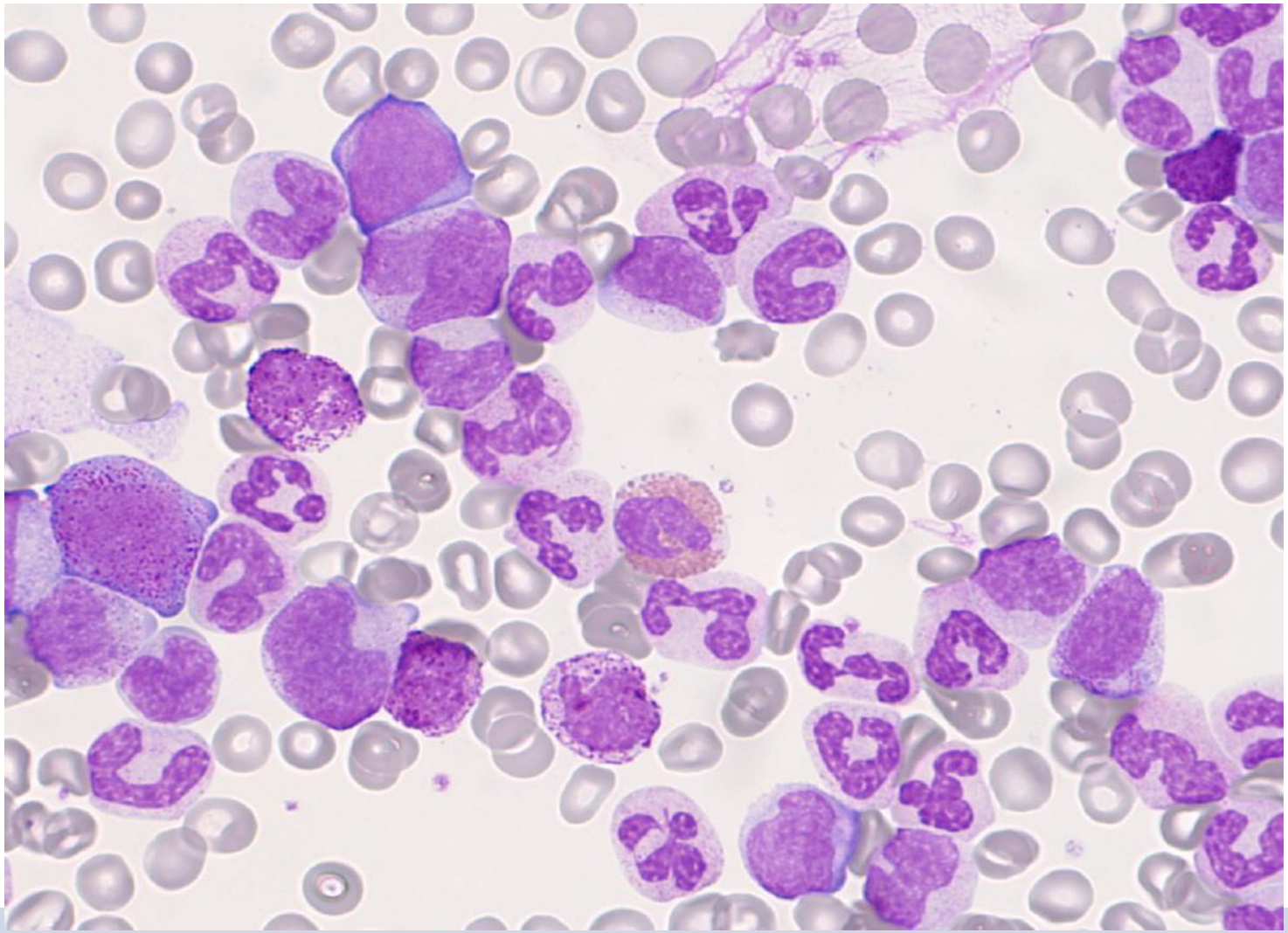
histologie

cytochemie
- myeloperoxydase of Sudan black kleuring
- non-specifieke esterase

Immunofenotypering

cytogenetica
- metafase analyse, FISH

moleculaire biologie
- PCR



May-Grunwald Giemsa

Gebruik van morfologie voor diagnose en classificatie

- Tellen van 500 cellen
  - % blasten versus alle kernhoudende cellen
- cytochemie
  - myeloperoxydase (MPO) of Sudan black B kleuring (SBB)
  - non-specifieke esterase (NSE) reactie
- myelodysplasie
  - % binnen cellijn
  - multi-lineage / uni-lineage
- ijzerkleuring
  - ring sideroblasten

Percentage blasten

AML en ALL : > 20% met uitzonderingen waar je geen 20% hoeft te halen (genetische afwijkingen, post therapie etc)

ICC ook AML

MDS RAEB: 5 -20% WHO 2016: MDS-EB 1 of 2 WHO 2022 MDS-IB 1of 2

- RAEB I: 5 -10%
- RAEB II: 10 -20%

Bij ICC is dit dan MDS/AML bij blast>10%
Behalve bij *BCR::ABL1*

andere MDS < 5 %

- Refractaire cytopenieen MDS-SLD/MLD MDS LB
- MDS met 5q- MDS met genetische afw
- MDS unclassifiable MDS-U
- kinder- MDS

ICC: nog wel SLD en MLD

Blasten: morfologische kenmerken

- middelgrote tot grote cellen
- basofiel cytoplasma, soms met enkele azurofiele granula of vacuoles
- perinucleaire opheldering
- Grote kern, rond of irregulair
- Fijn tot iets grover nucleair chromatine
- prominente nucleoli

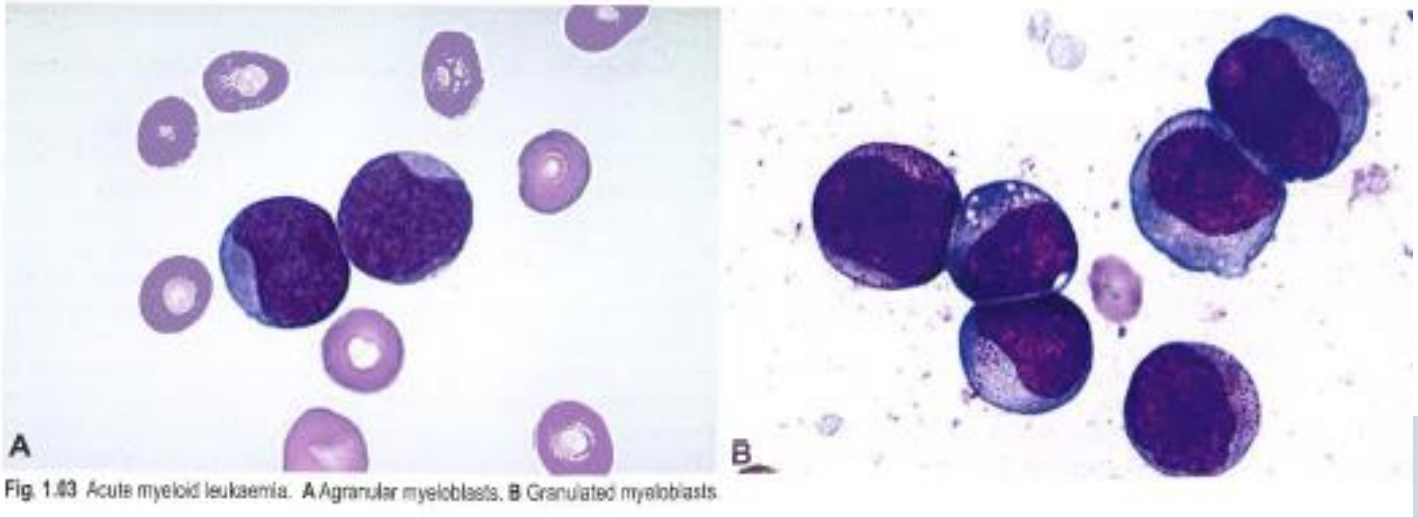
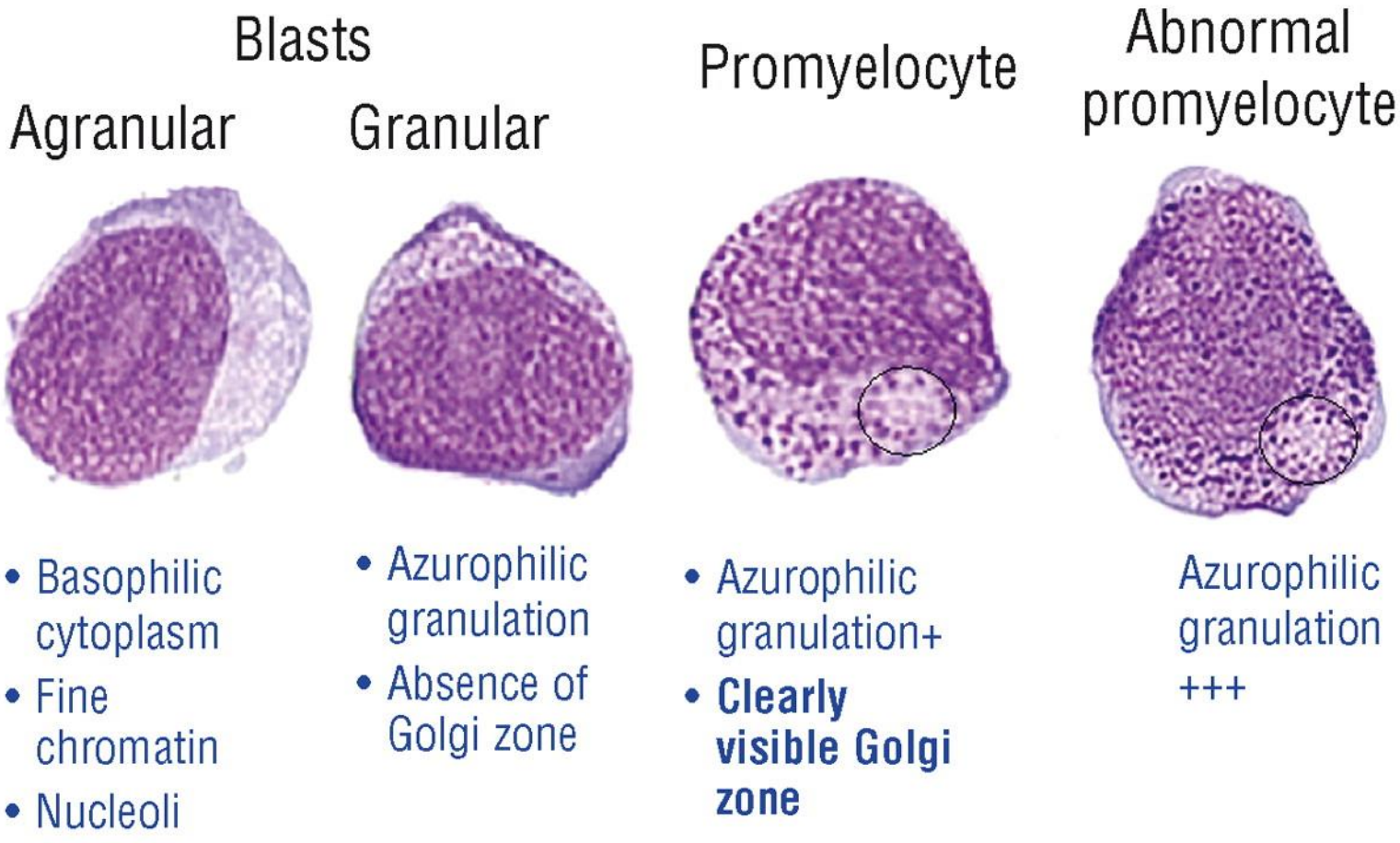


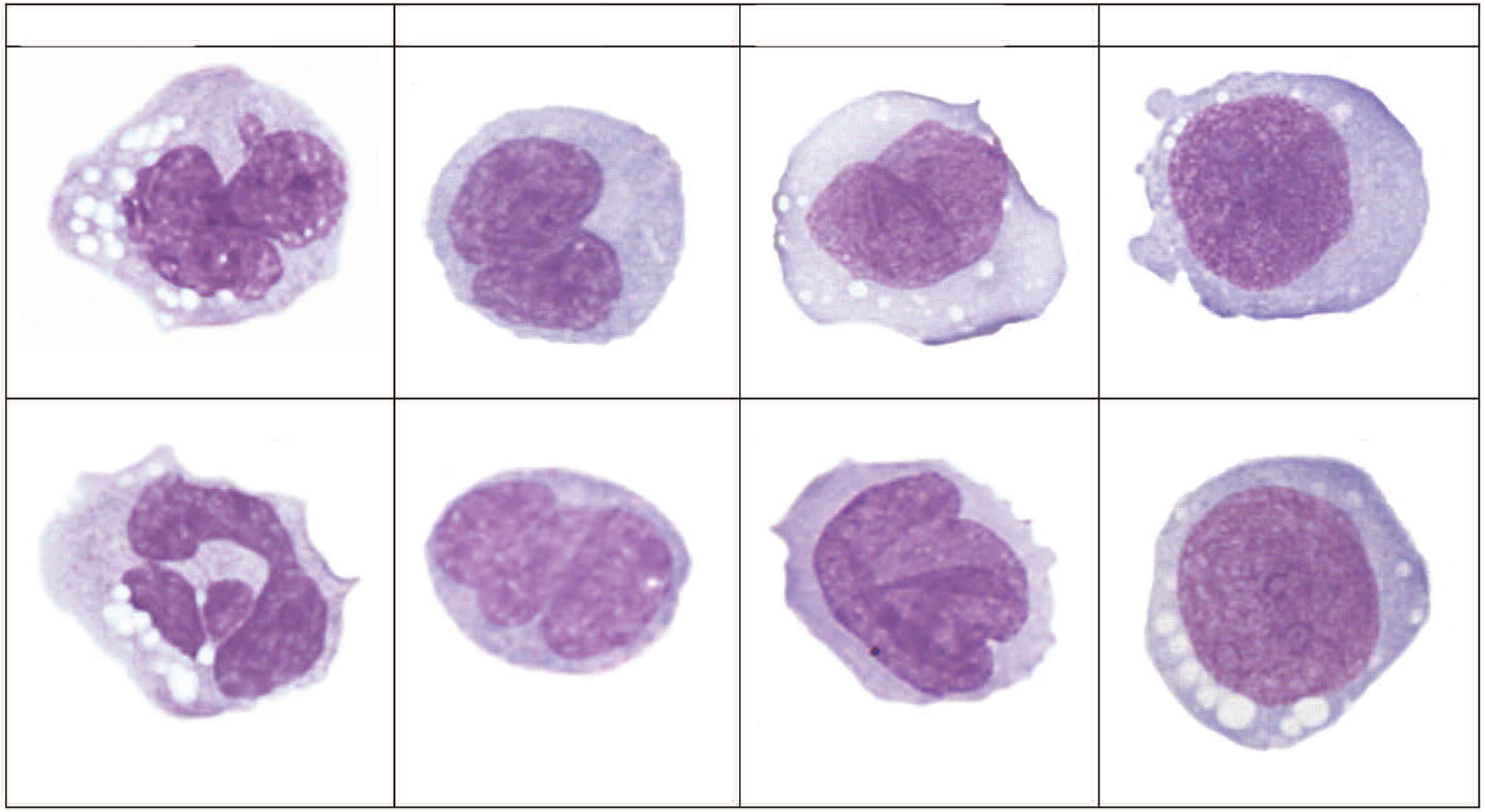
Fig. 1.83 Acute myeloid leukaemia. A Agranular myeloblasts. B Granulated myeloblasts

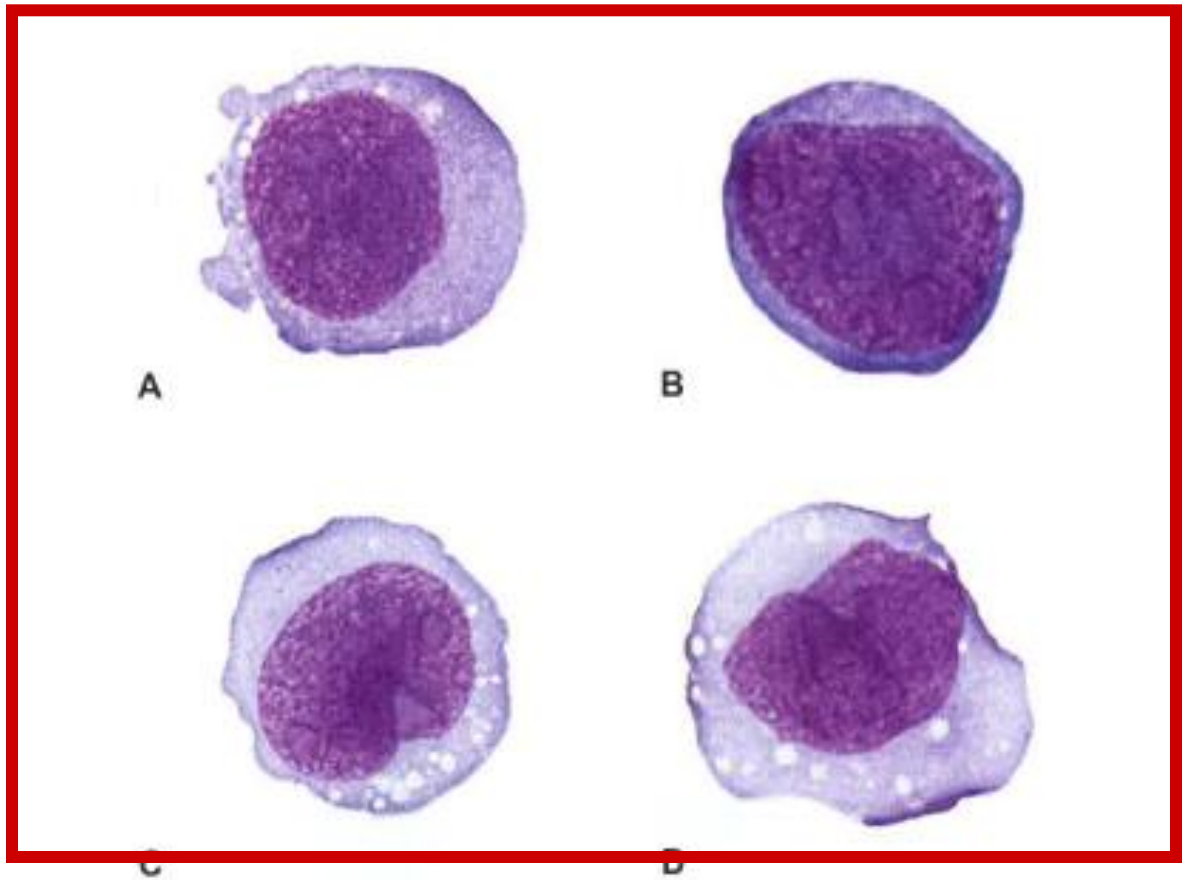
Blast of promyelocyt?

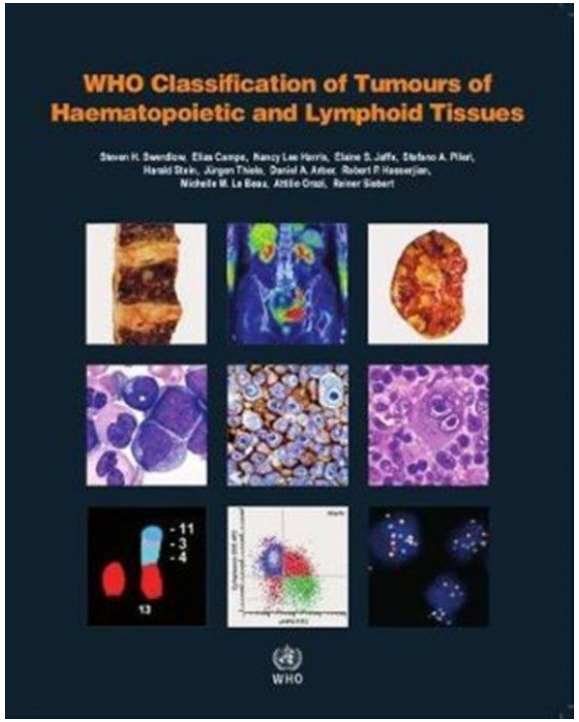


Mufti G J et al. Haematologica 2008;93:1712-1717

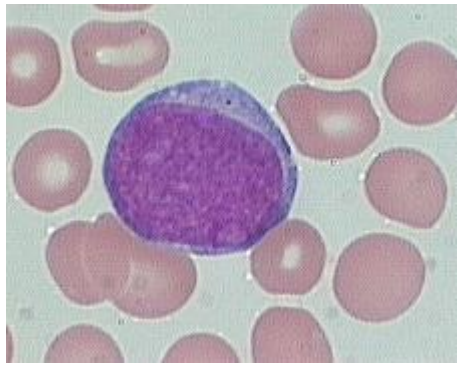
Monocyt of monoblast?
Kijk naar: kernvorm, kernstructuur, kleur cytoplasma, celgrootte

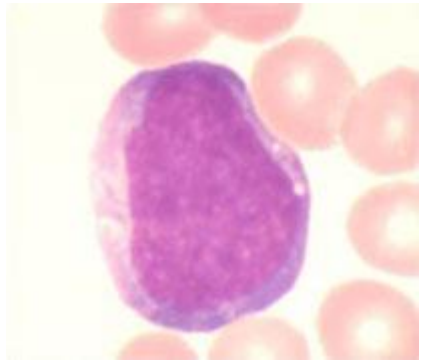


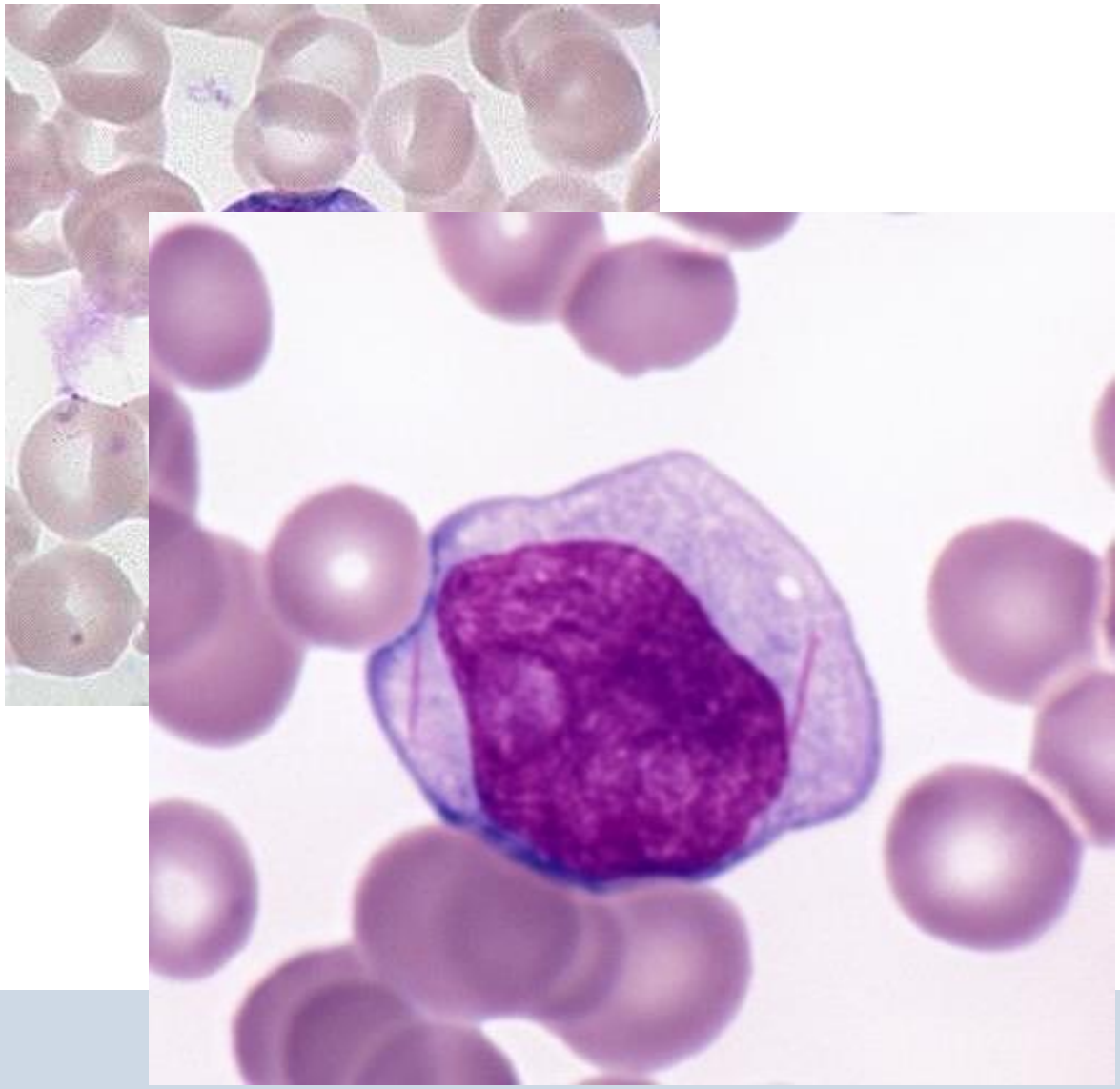

A
B
C
D
E
F


WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues
WHO

Lymfoblast of myeloblast??







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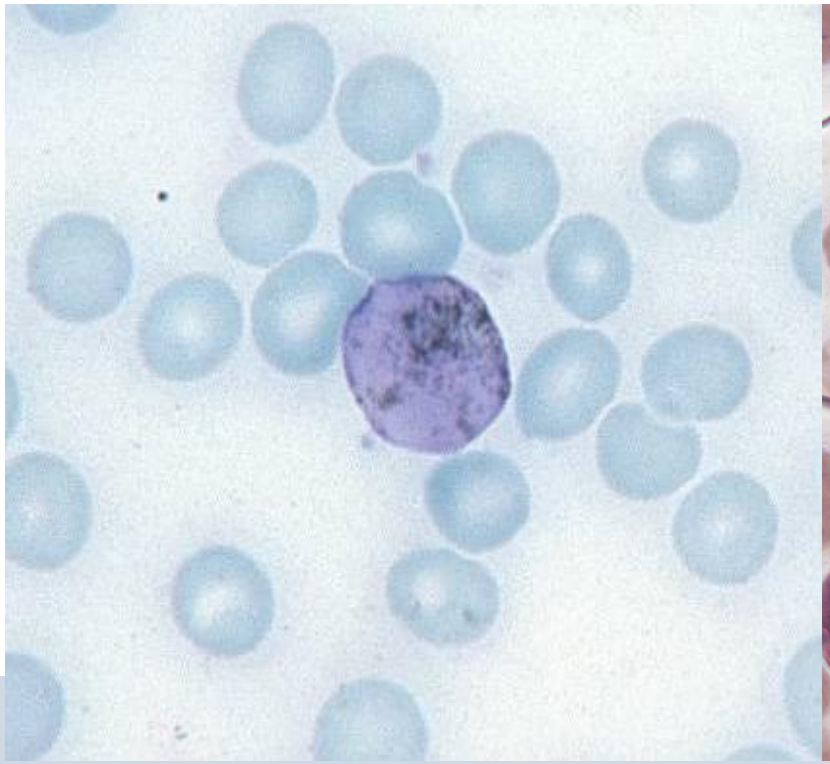
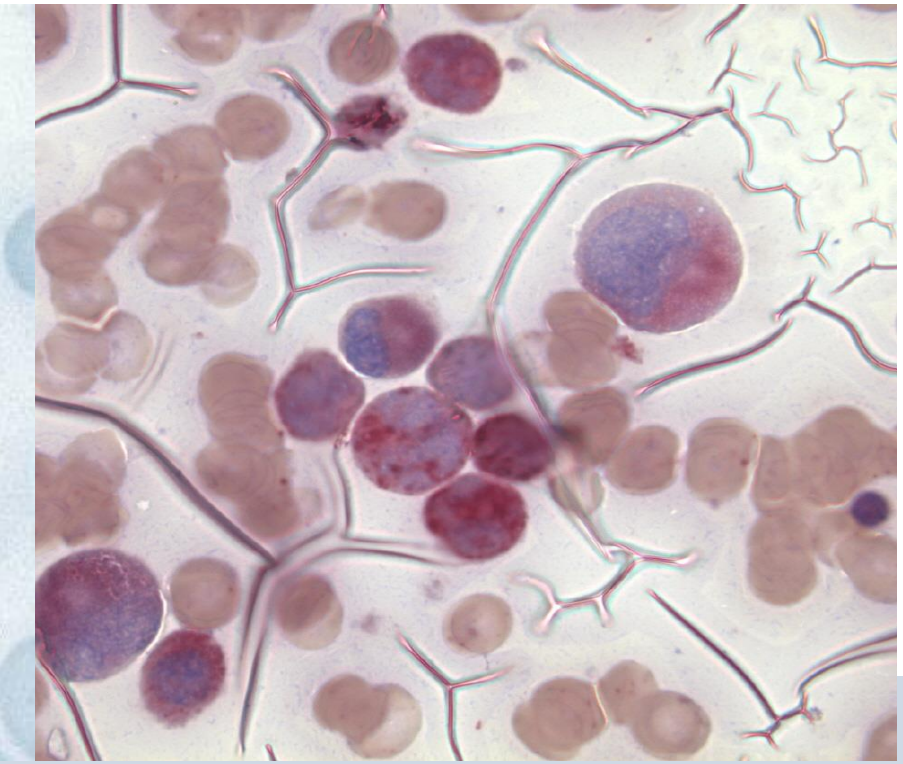
Cytochemie

myeloperoxydase reactie of Sudan black reaction is positief in myeloide cellen (sterk) en monocyten (zwak)

non-specifieke esterase reactie is positief in monocytaire cellen (diffuus in cytoplasma)





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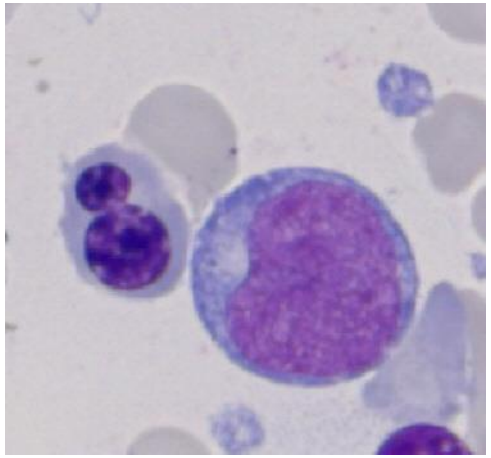
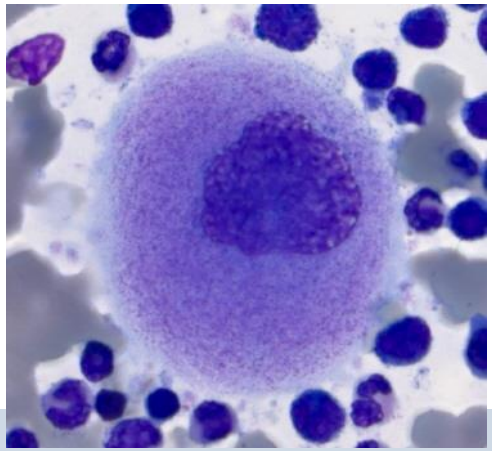
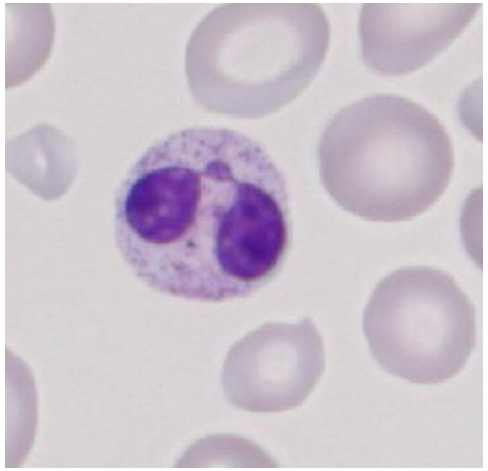
myelodysplasie

Voor AML: 2016: >50% in 2 cel lijnen *of* VG van MDS *of* MDS gerelateerde cytogenetische veranderingen
2022 : niet meer nodig voor diagnose AML myelodysplasie gerelateerd







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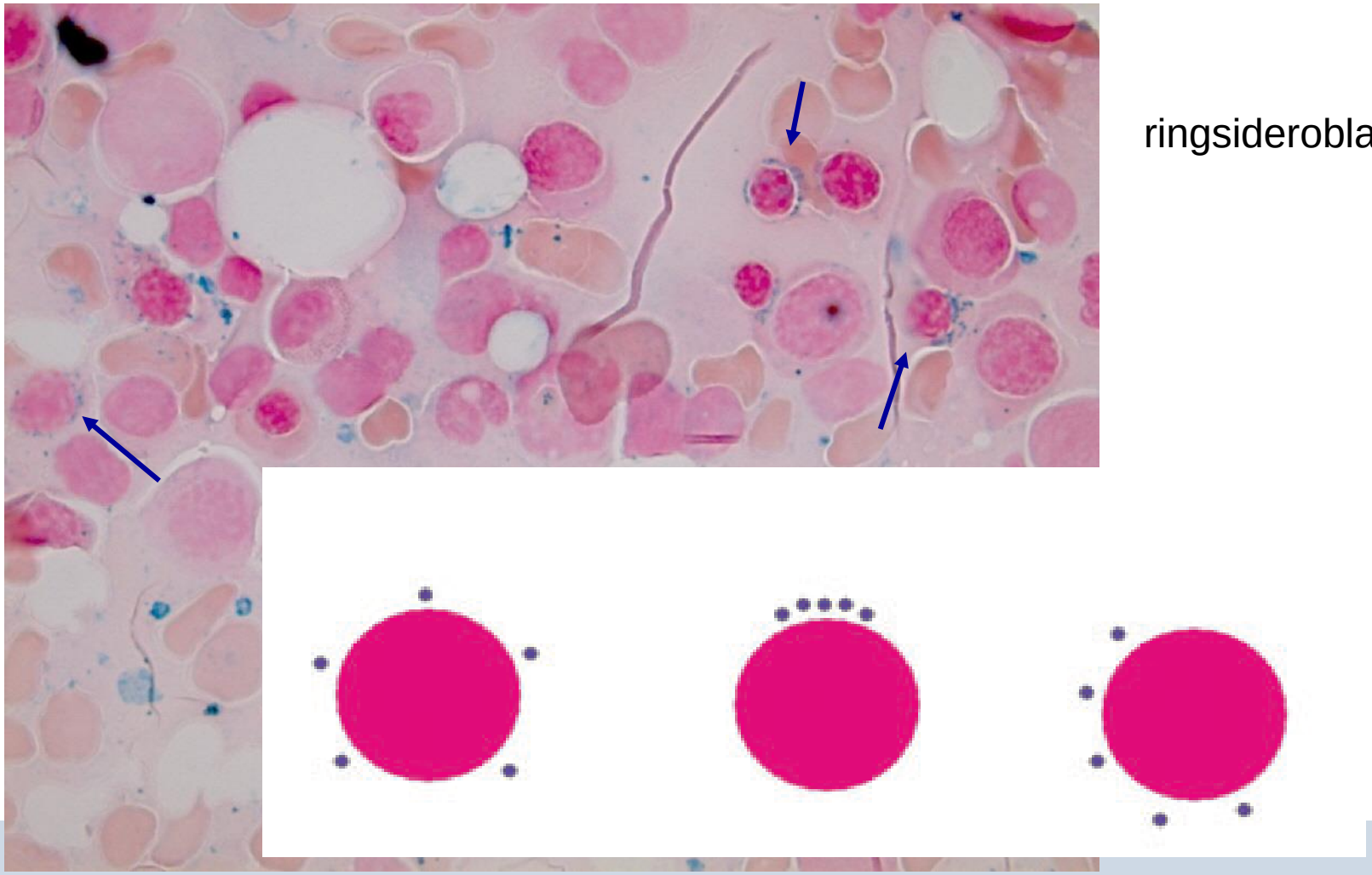
ijzerkleuring



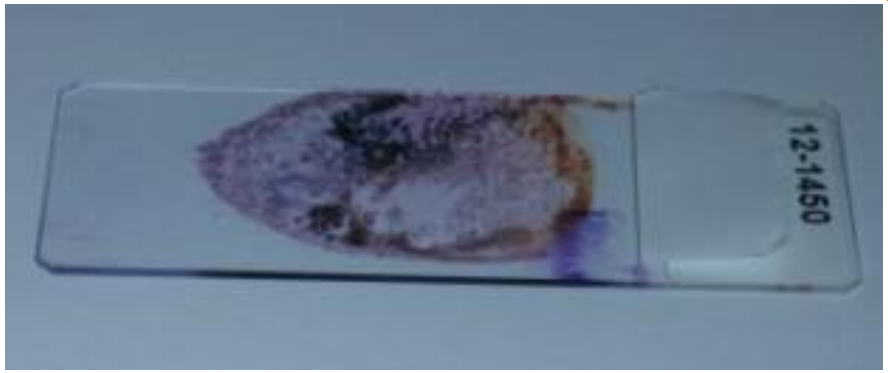
ringsideroblast

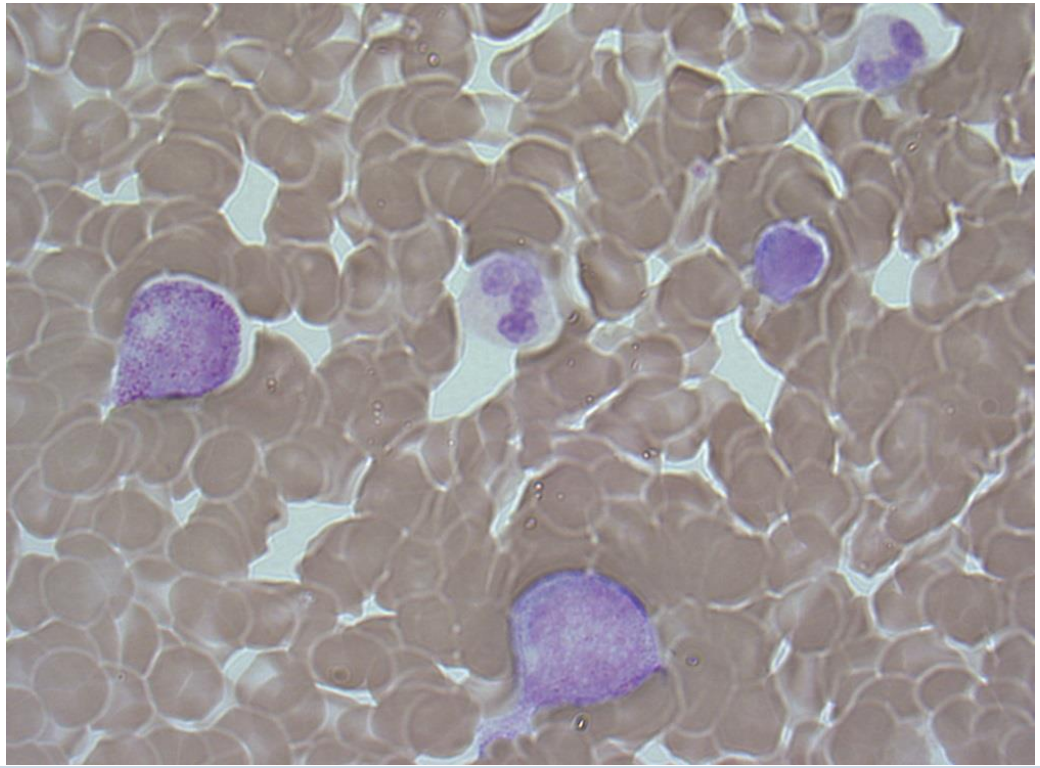
Rol van de morfoloog anno 2022

2022

- Kwaliteit van sample
- Criteria voor diagnose (% blasten)
- ~~Criteria voor klassificatie (dysplasie)~~
- Aanvullend onderzoek sturen

soms slechte uitstrijkjes..





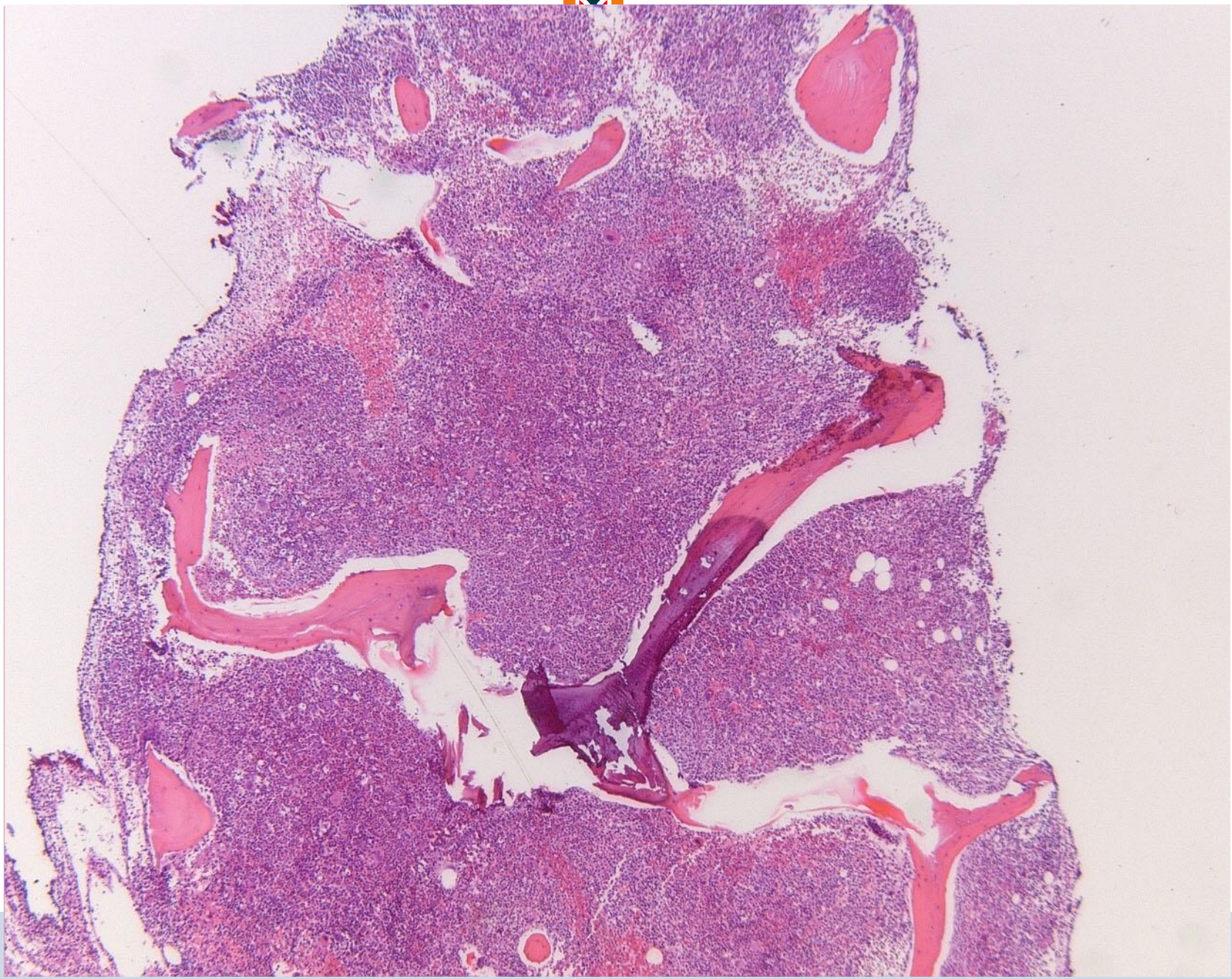
Je vraagt je dan af wat ermee is gebeurd

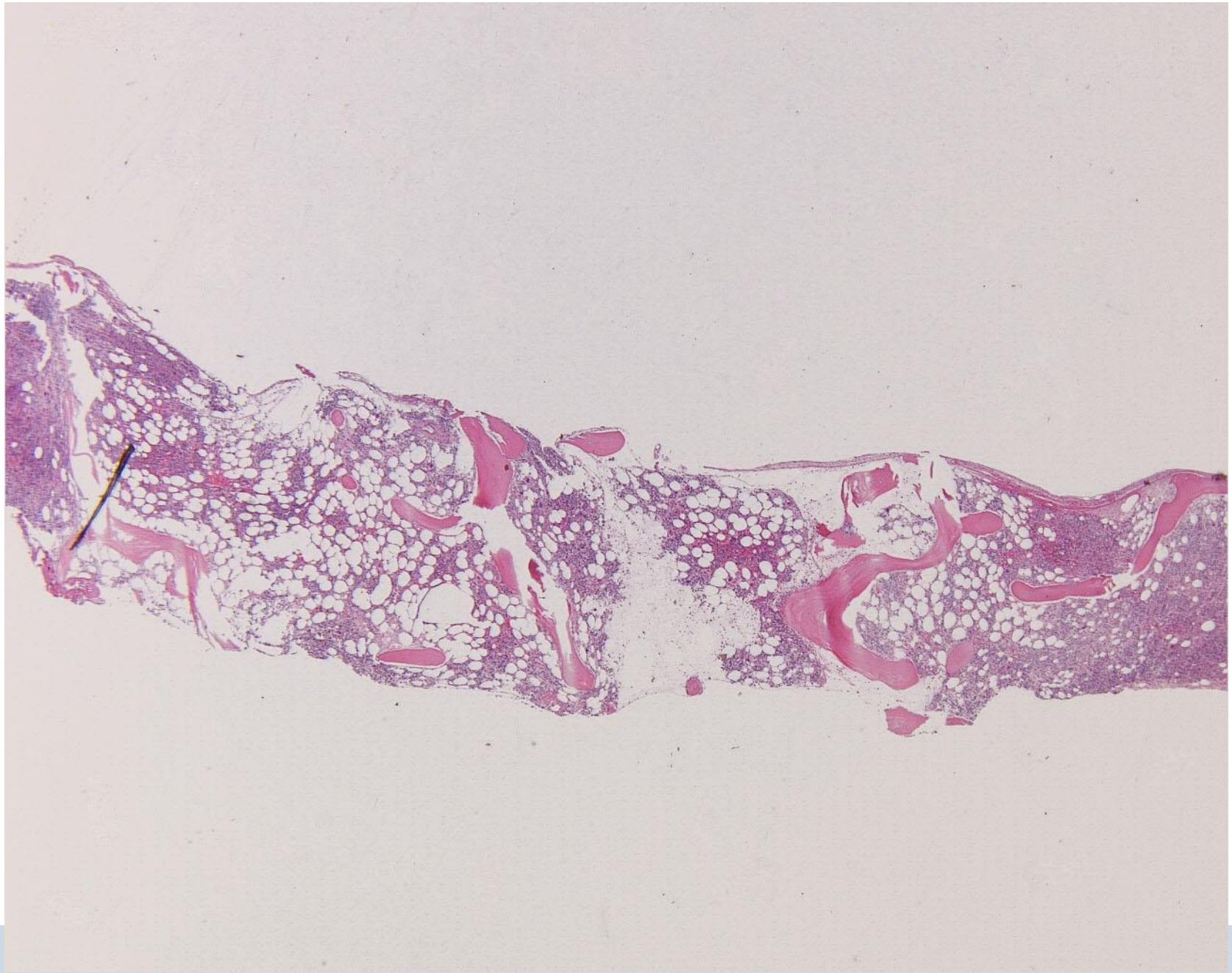
Bedenk: kan ik hierop een diagnose stellen of is het te slecht materiaal?
Kan aanvullend onderzoek nog extra informatie geven

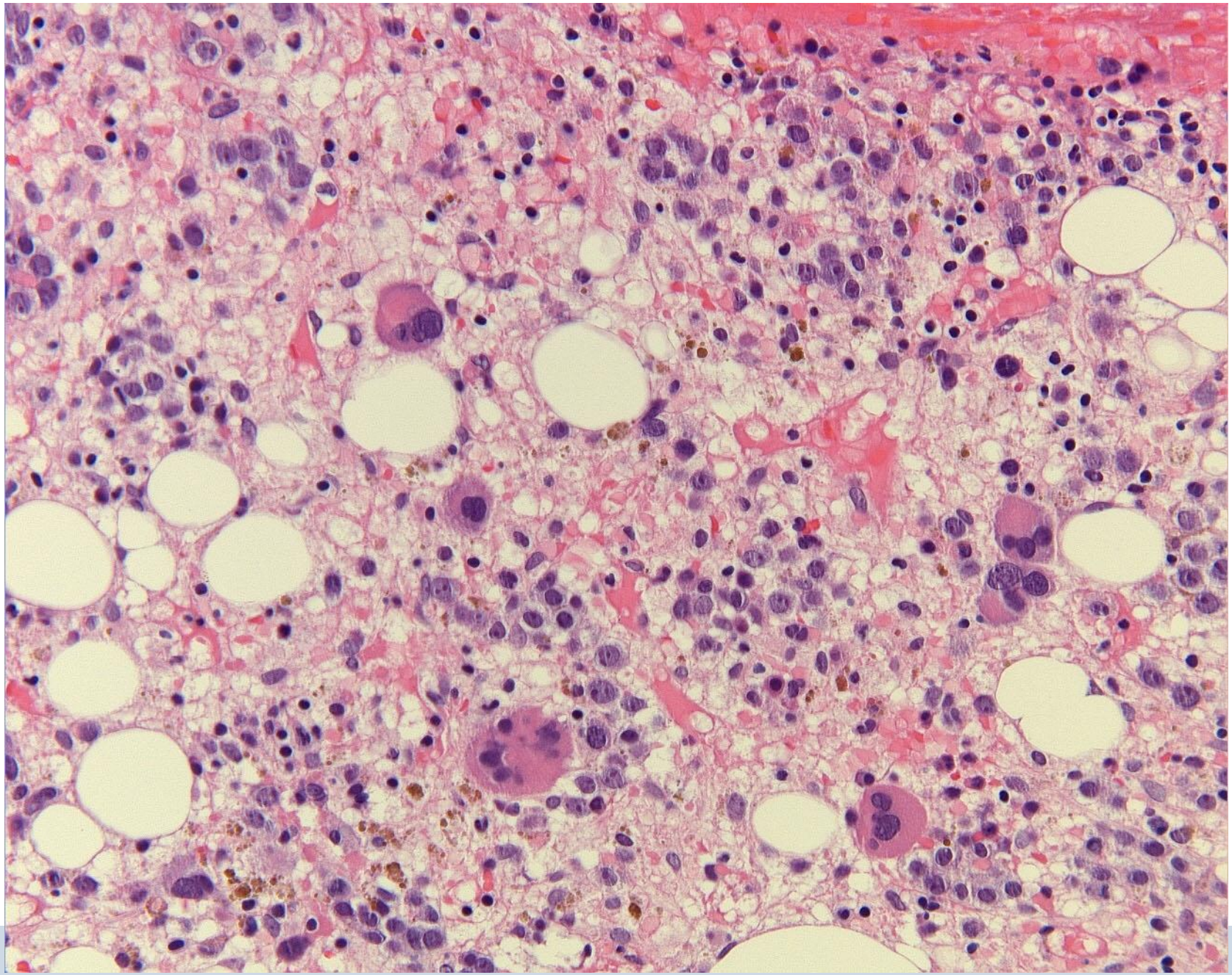
Wanneer een botbiopt

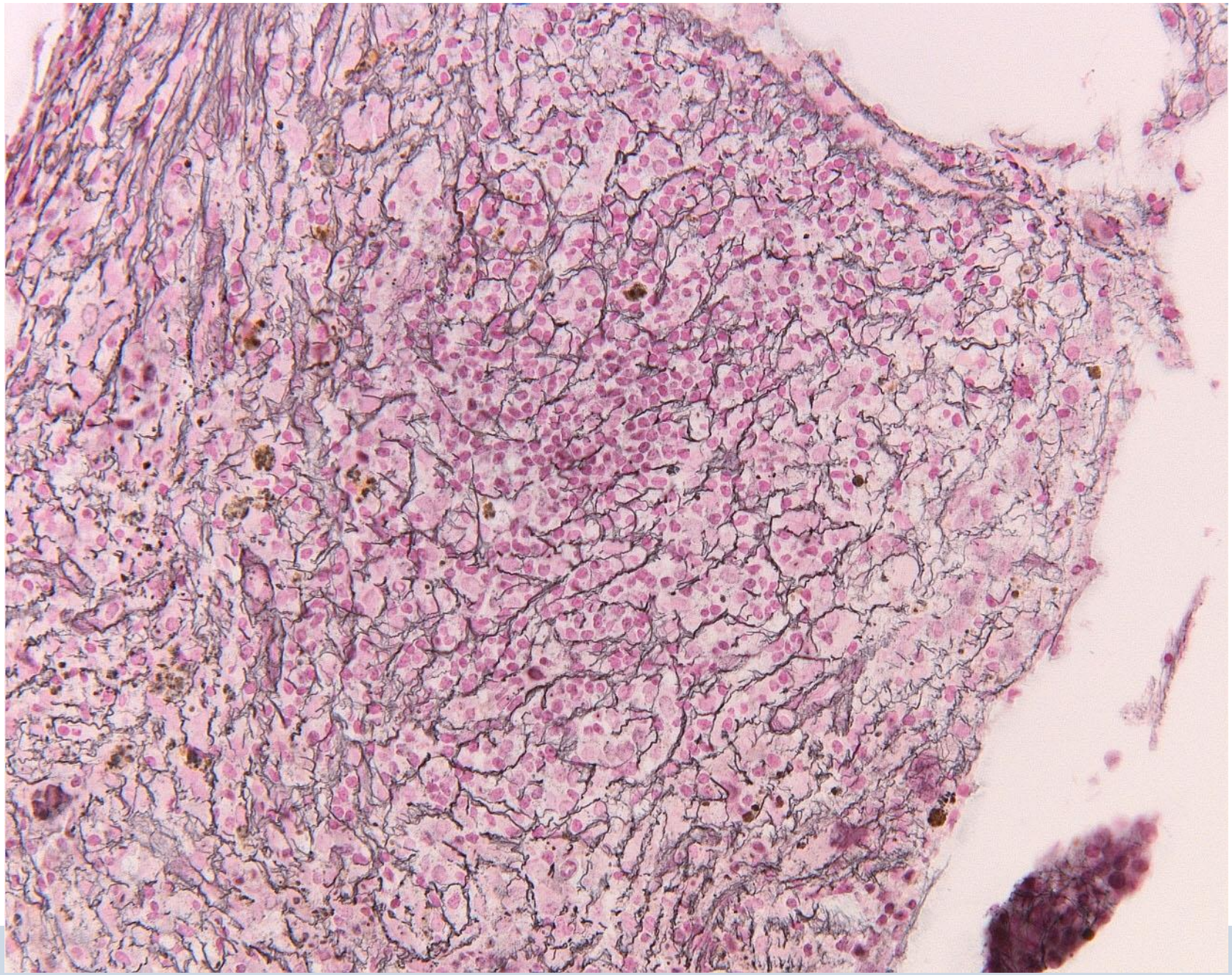
-altijd doen bij diagnose: wanneer de diagnose AML nog niet zeker is, ook om andere diagnoses te kunnen stellen, bv solide tumoren.
-in geval van dry tap

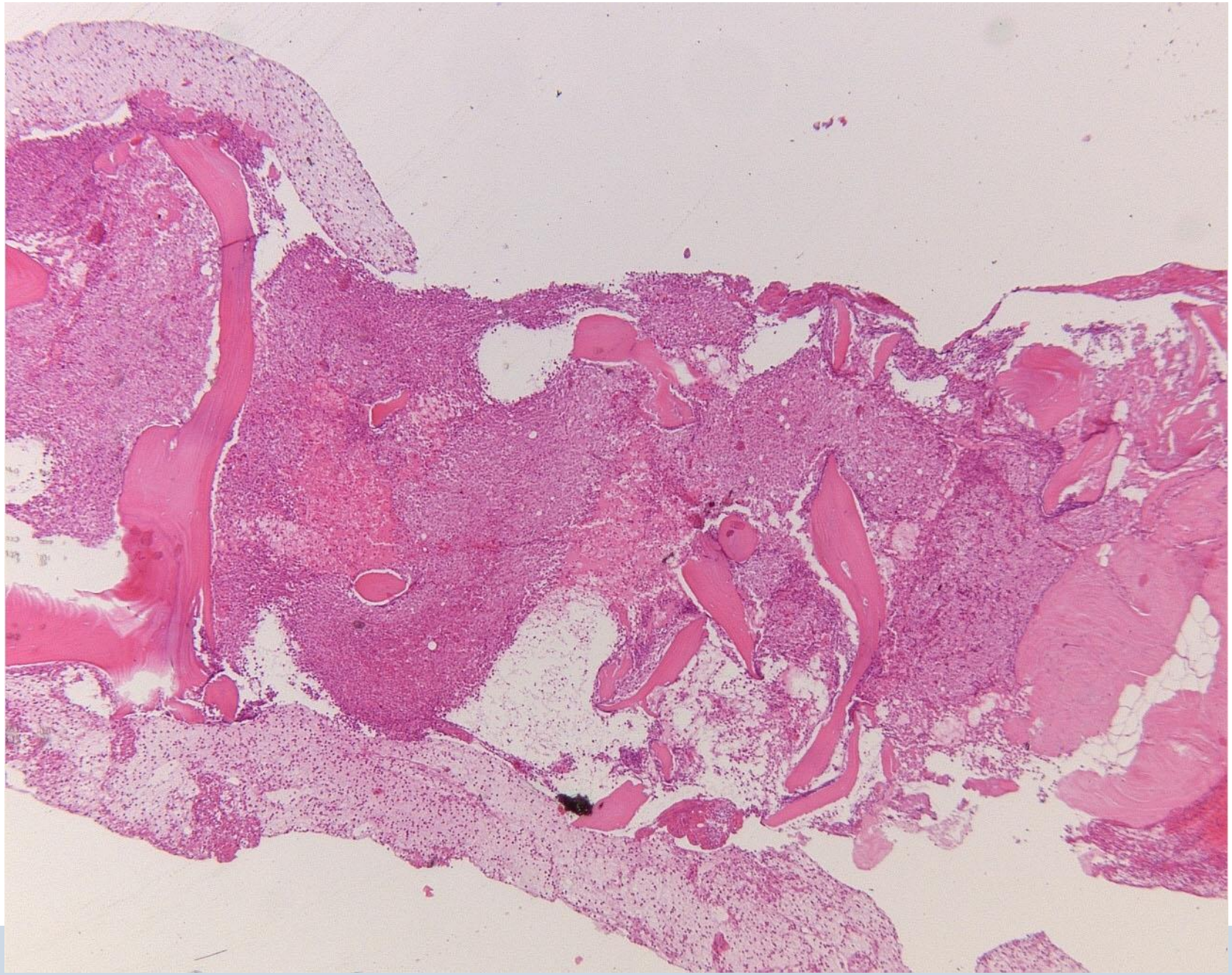
Let op!
-waar herken je blasten aan? Soms CD34-
-uitrijping of gebrek daaraan
-dysplasie, fibrose

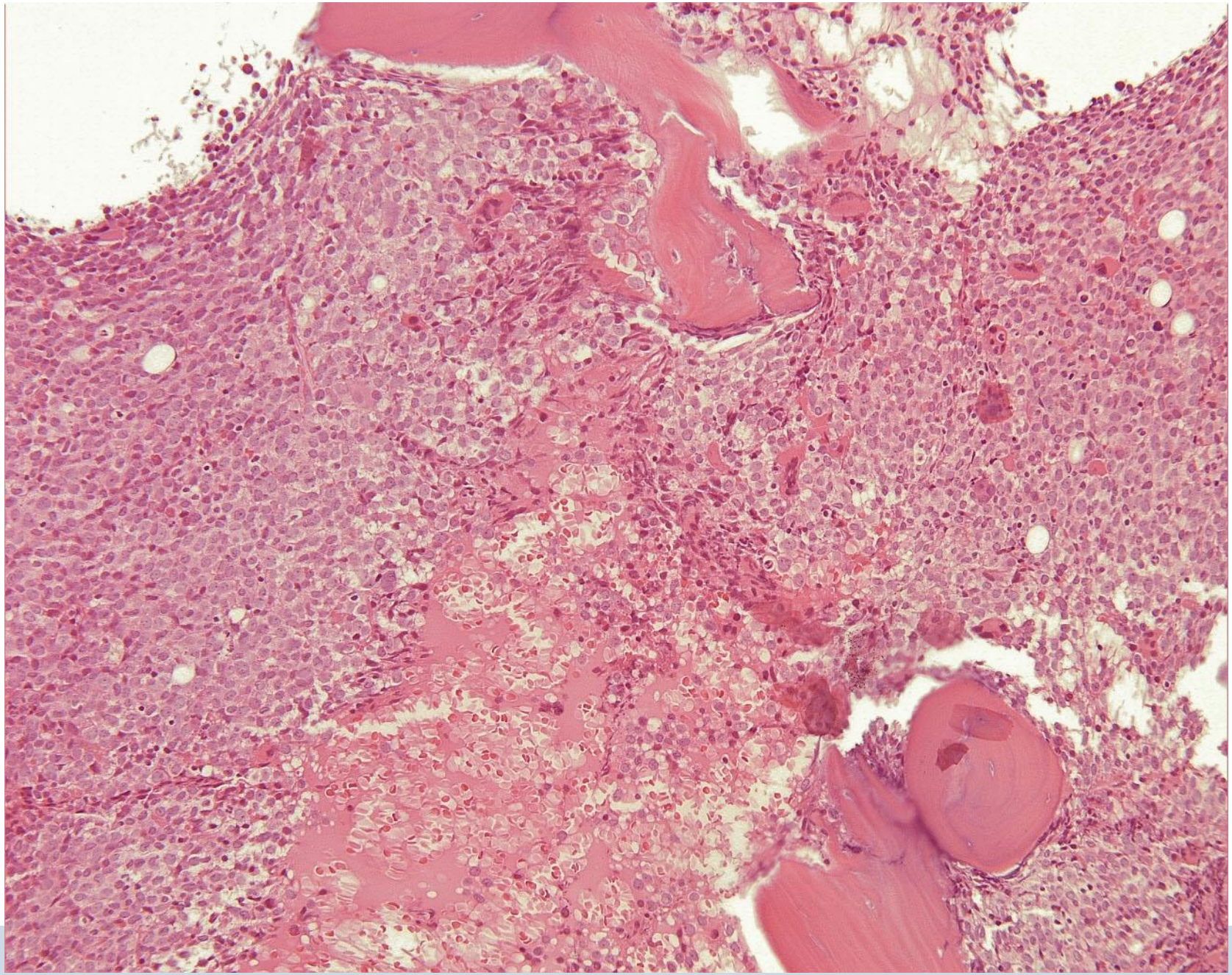


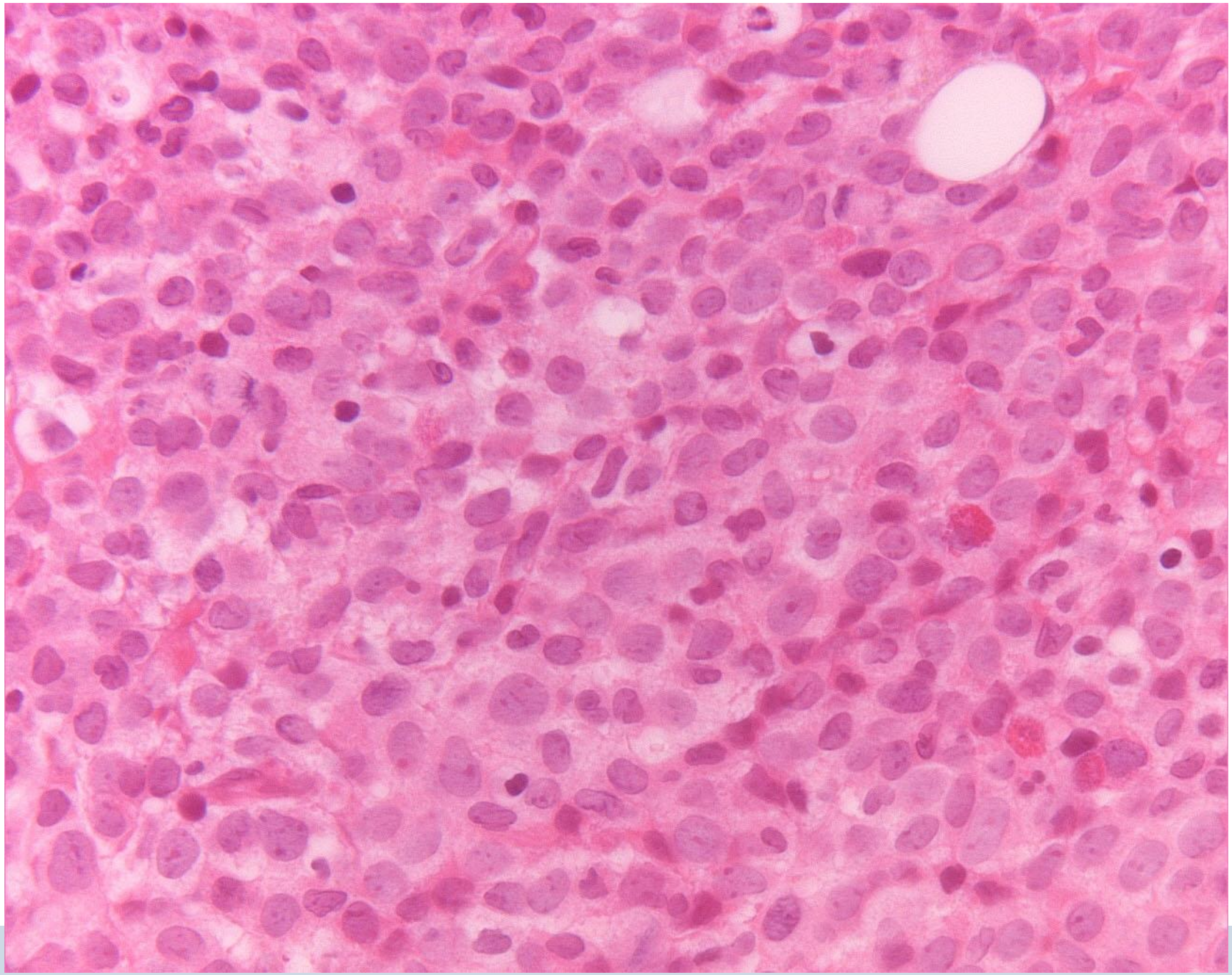




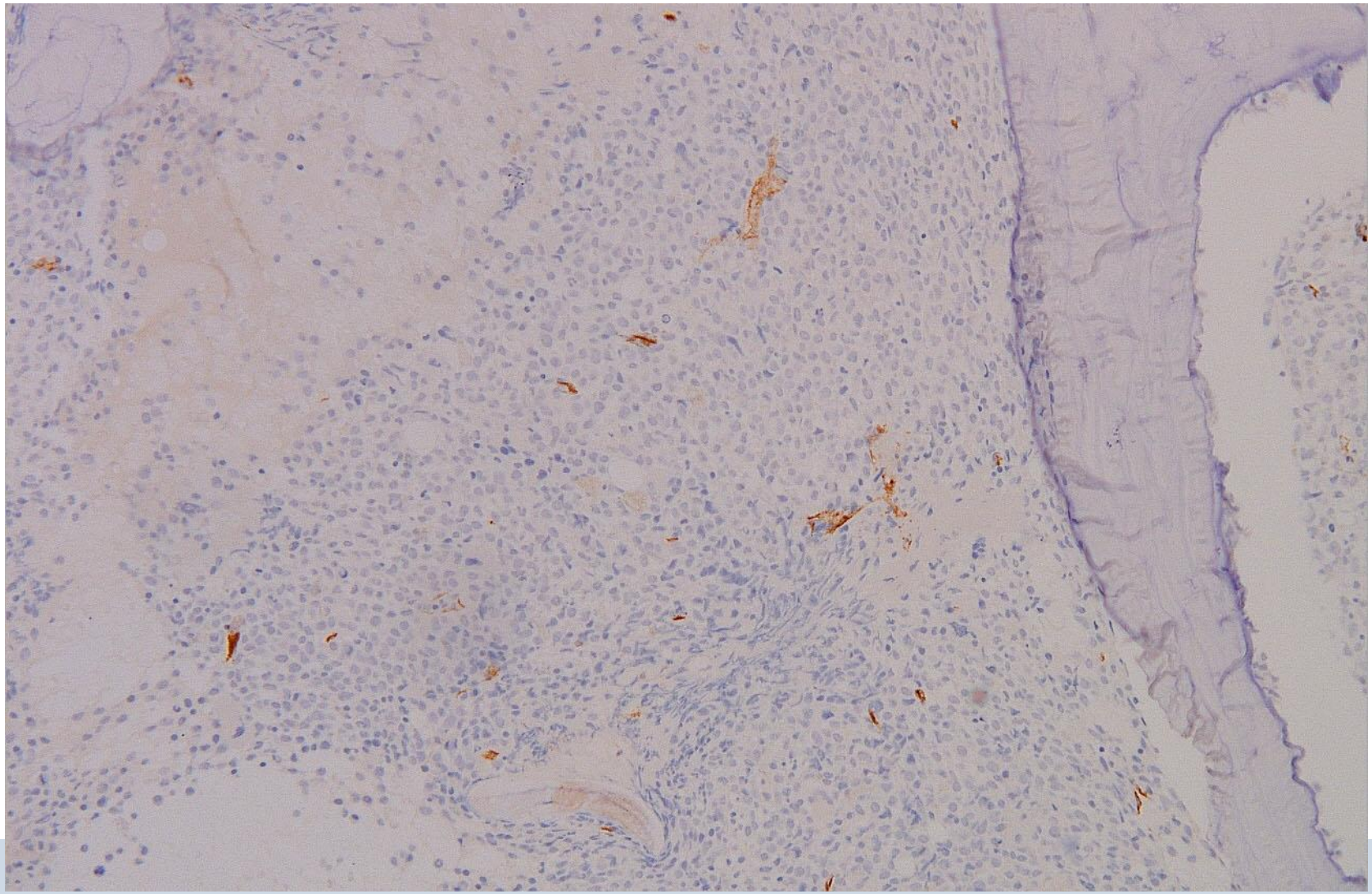




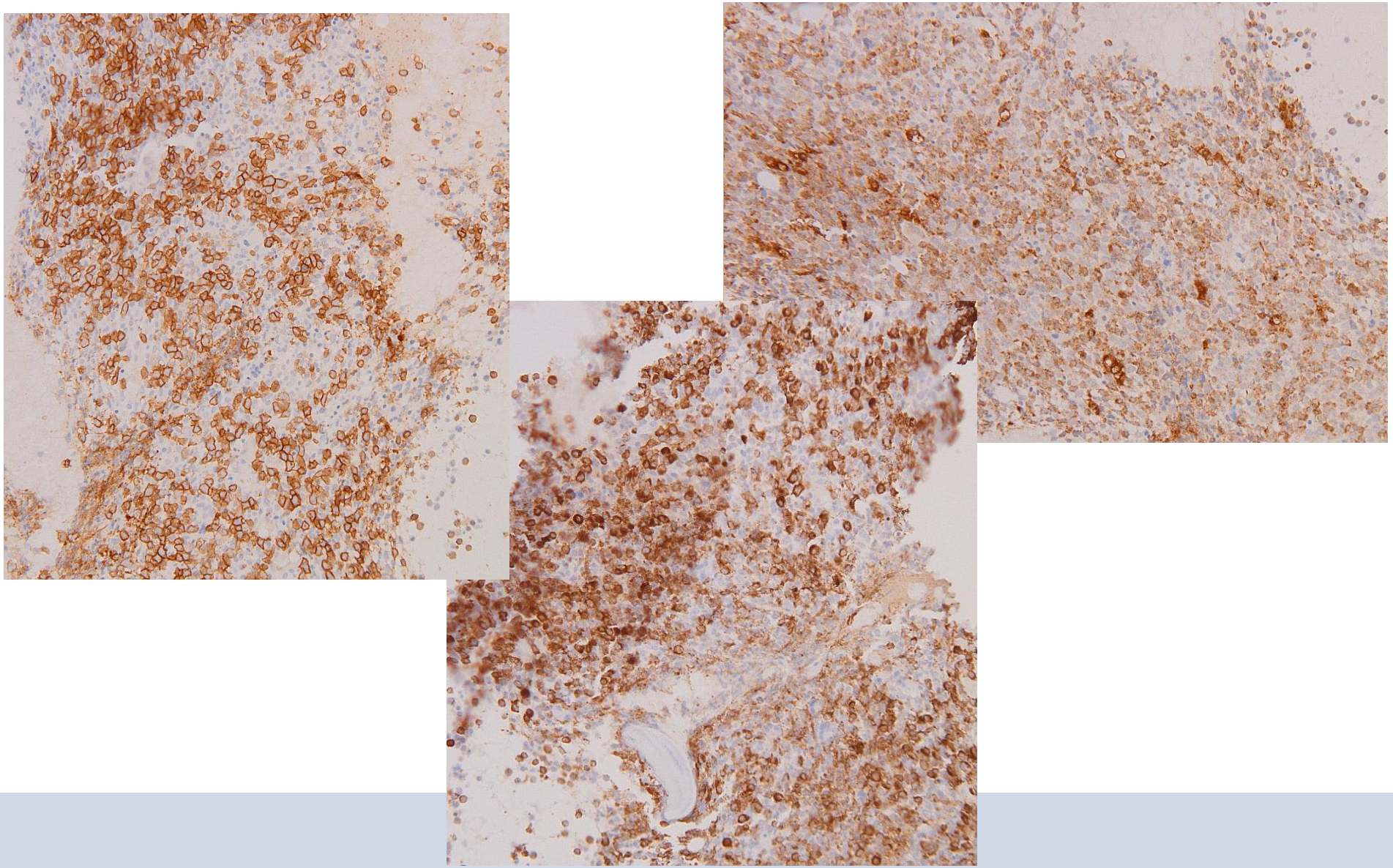




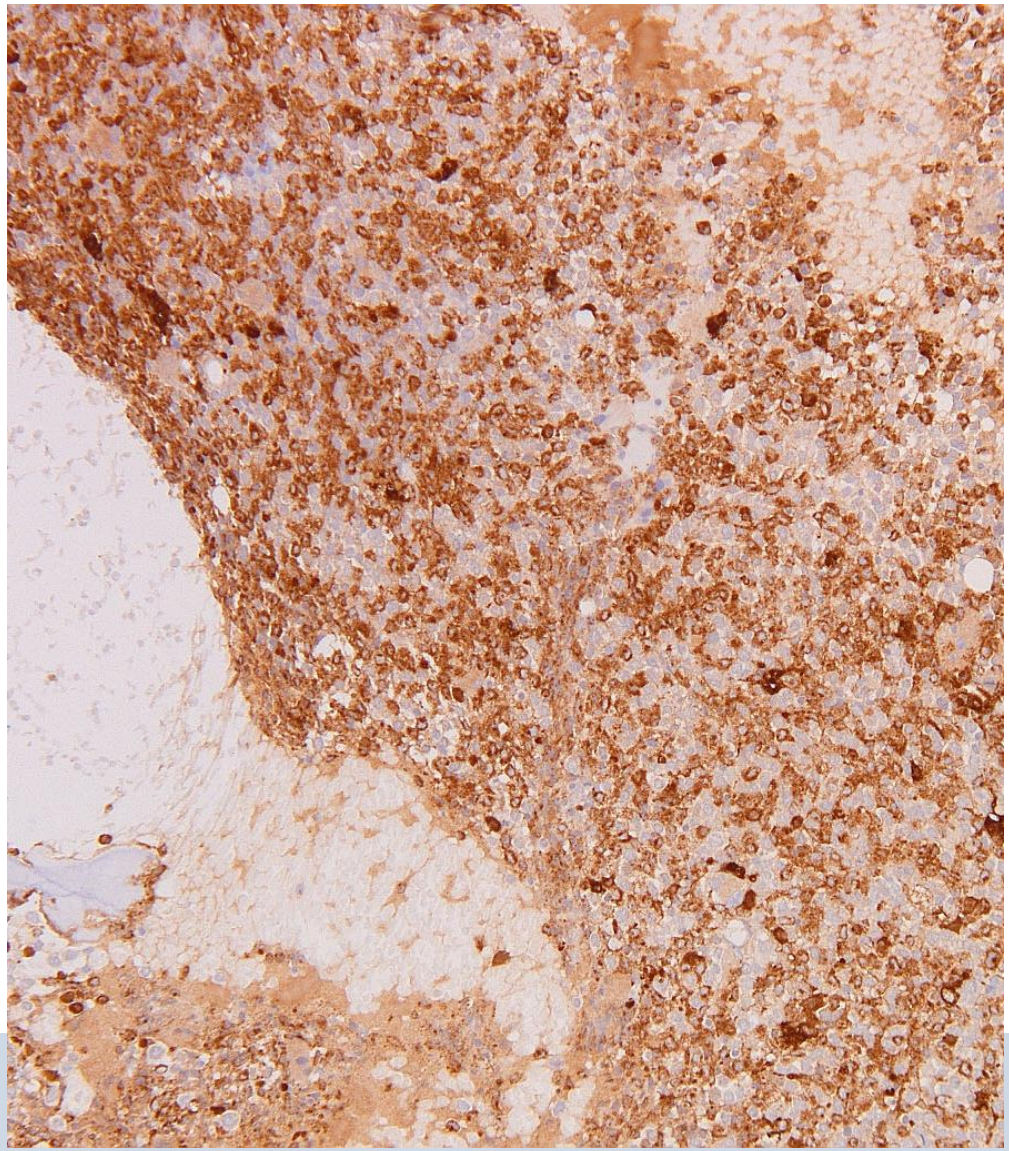
CD34

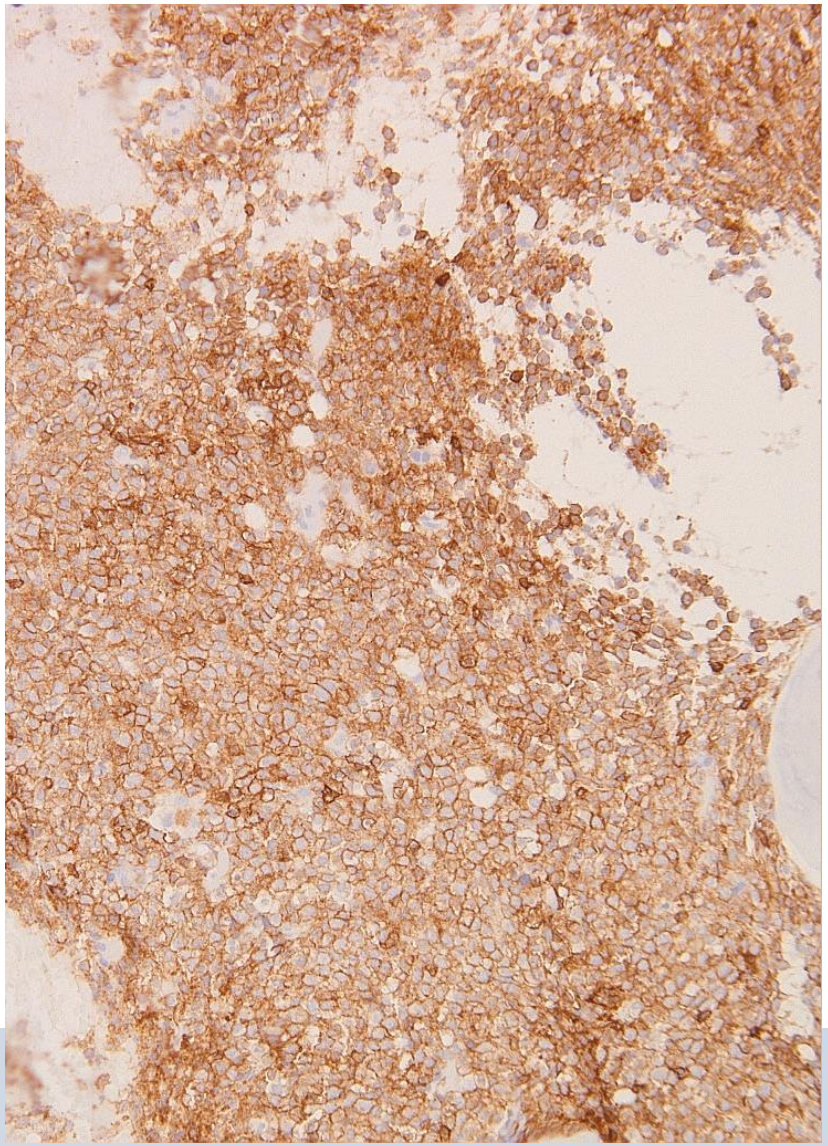


CD117, MPO en CD68



Lysozym en CD45





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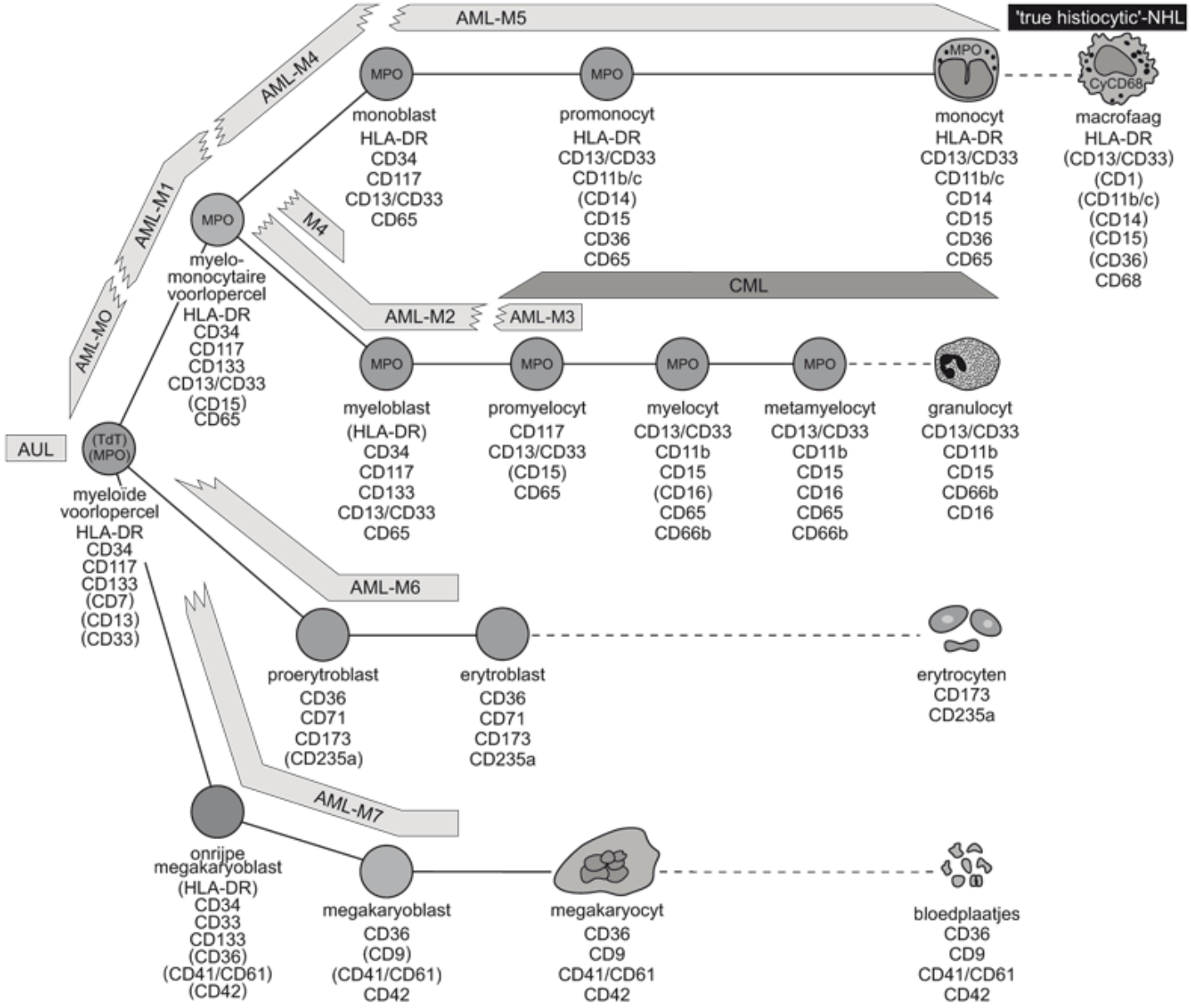
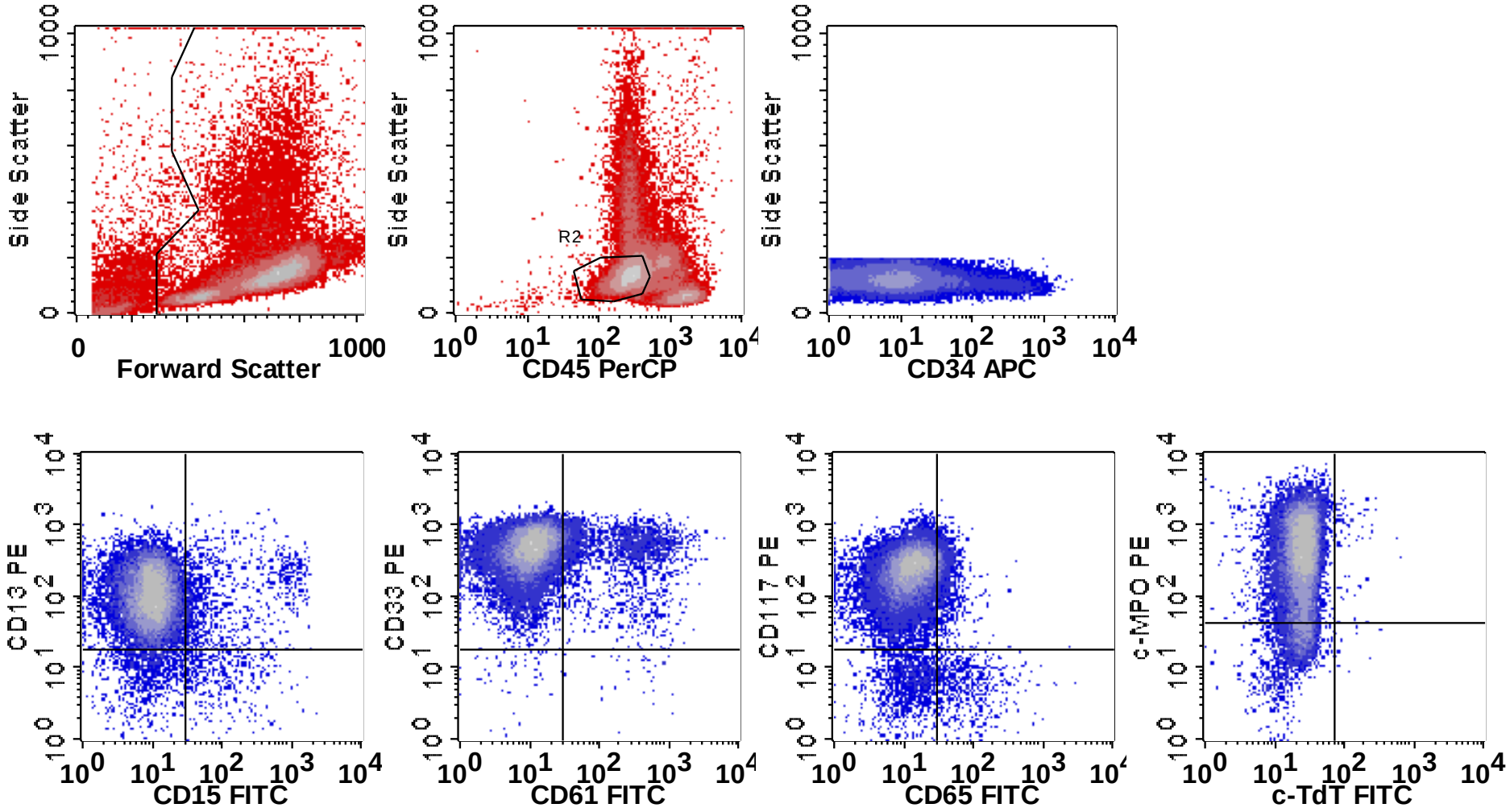


voorbeeld


Side Scatter
Forward Scatter
CD45 PerCP
R2
CD34 APC
CD13 PE
CD15 FITC
CD33 PE
CD61 FITC
CD117 PE
CD65 FITC
c-MPO PE
c-TdT FITC

Immuunfenotypering en acute leukemie
Minimale residuale ziekte detectie

Oppervlakte kenmerken die niet op normale cel thuishoren, specifiek voor de leukemie:

LAP=leukemia associated phenotype

Bijvoorbeeld CD7 op AML

Rol immunofenotypering bij diagnose AML/MDS

- Klassificatie: MPO-negatieve AML
- Prognose: -
- MRD detectie
- Therapie: anti-CD33, ..
- MDS: voor diagnose: in gebruik, voor prognose: experimenteel

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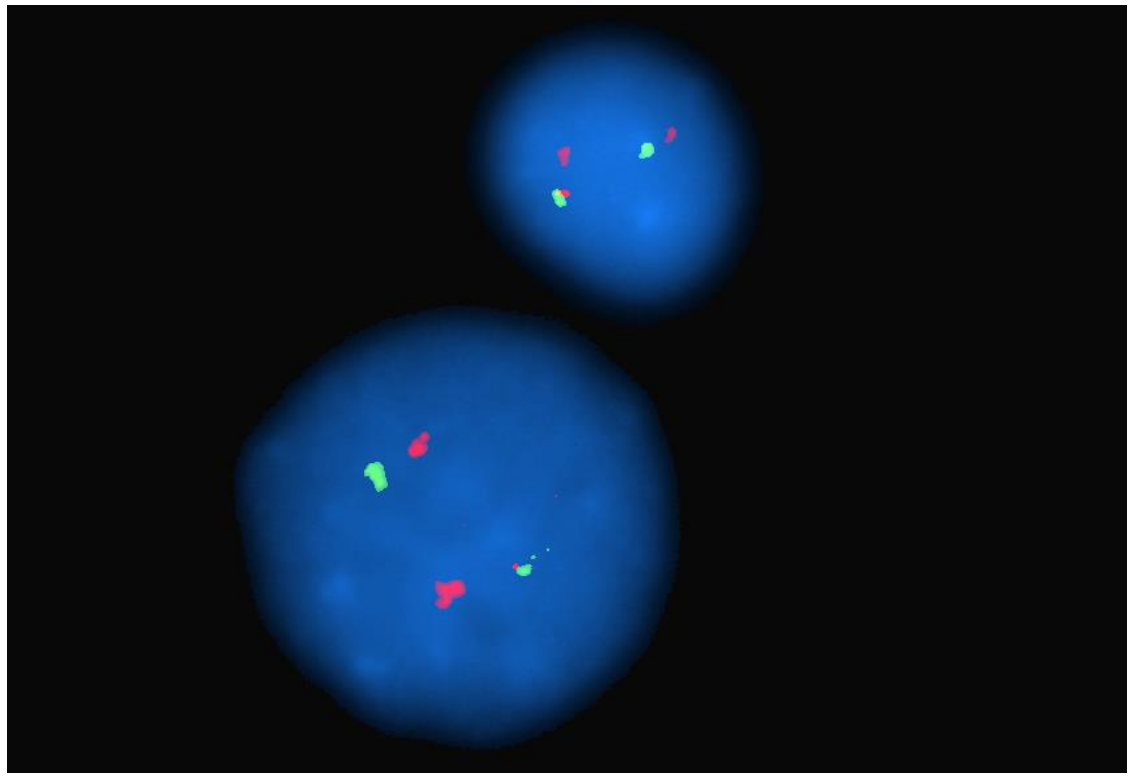
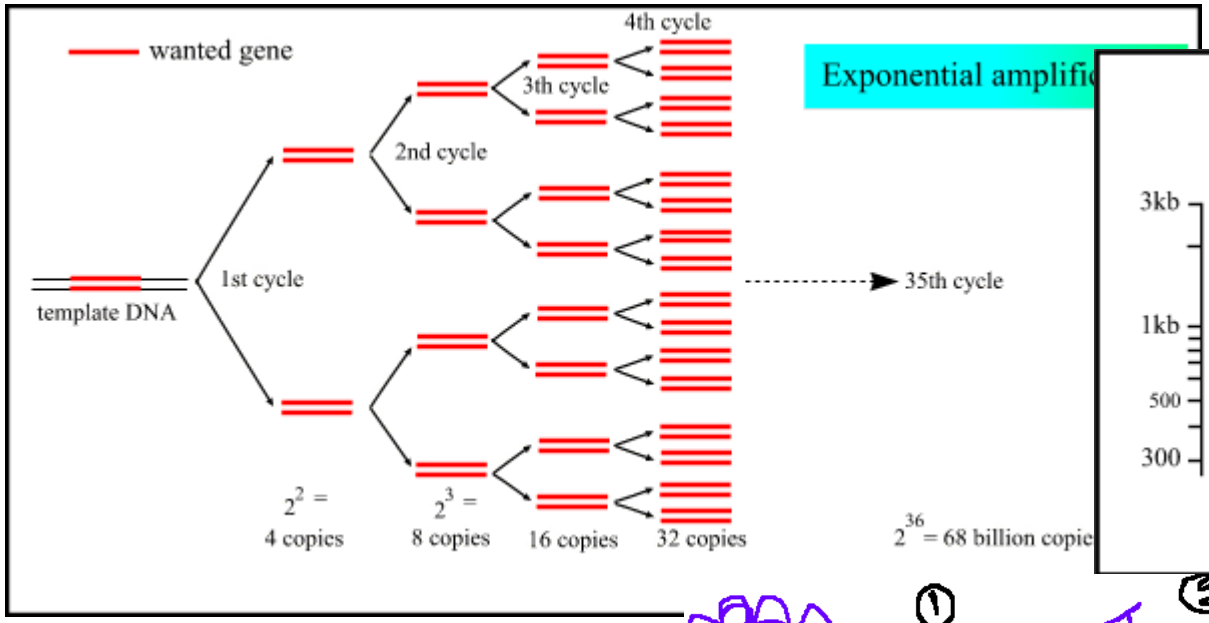
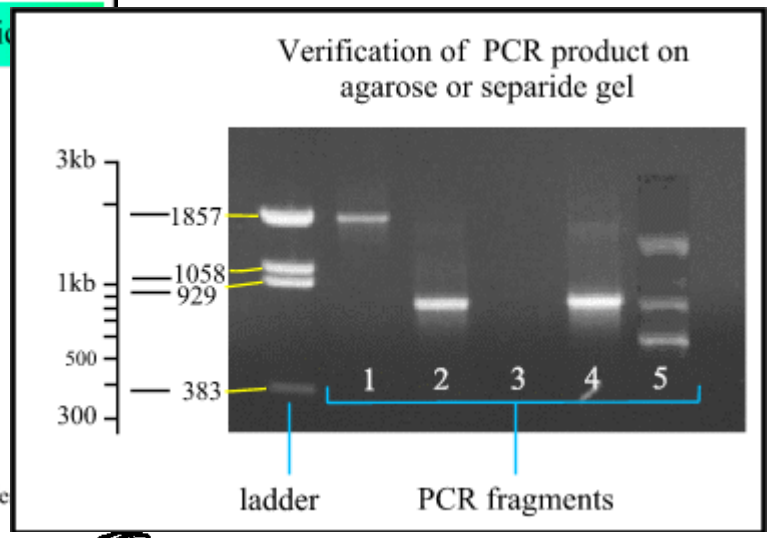
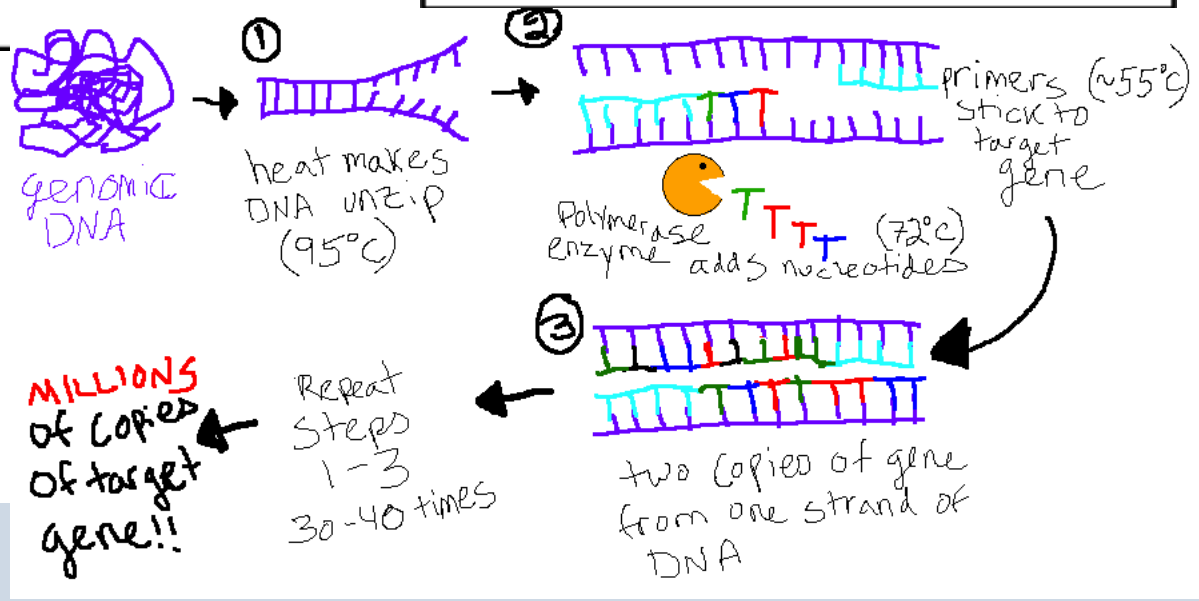


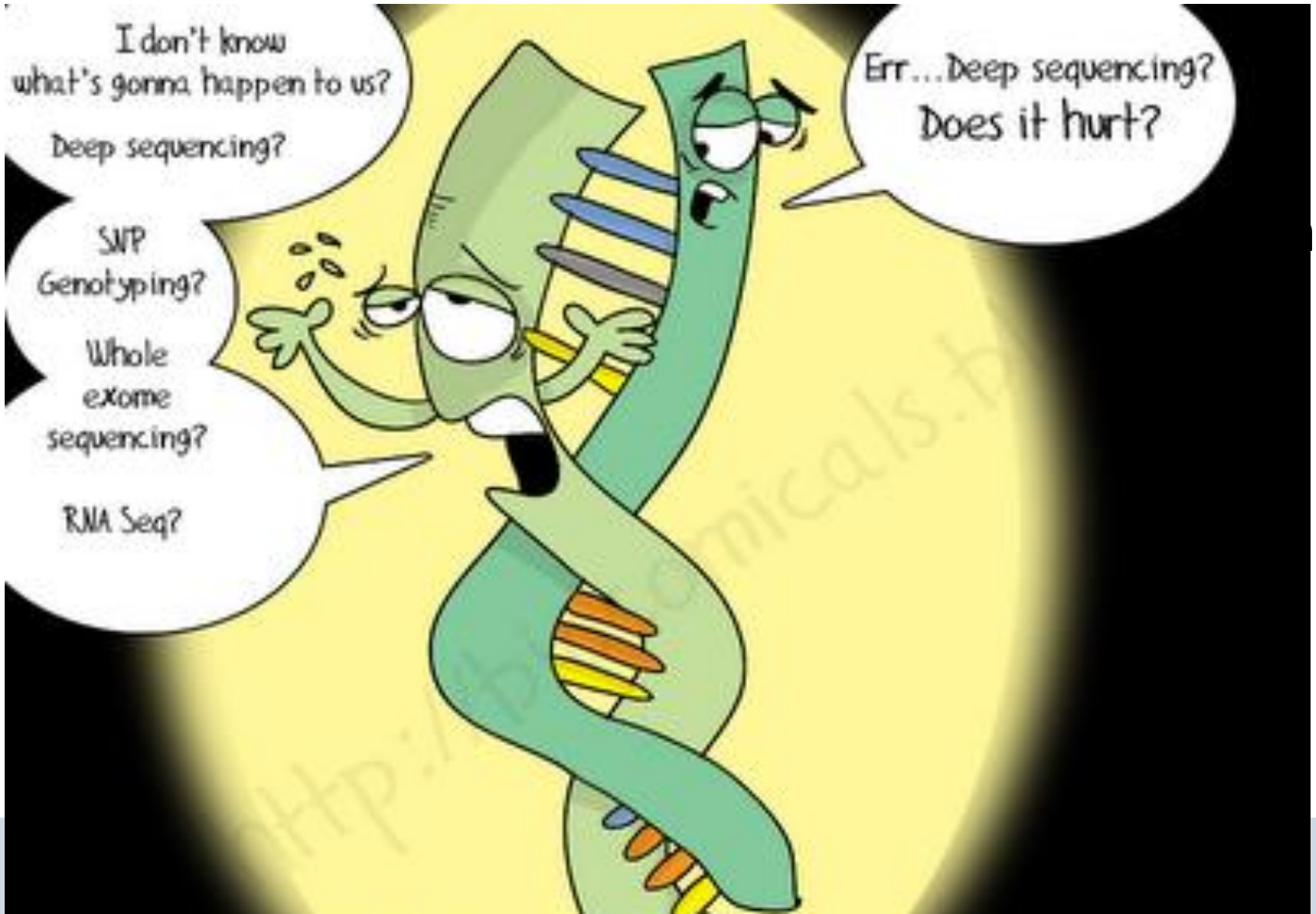
Diagnostische methoden: PCR







Rol cytogenetica/moleculaire diagnostiek bij diagnose AML/MDS



ELN risk stratification

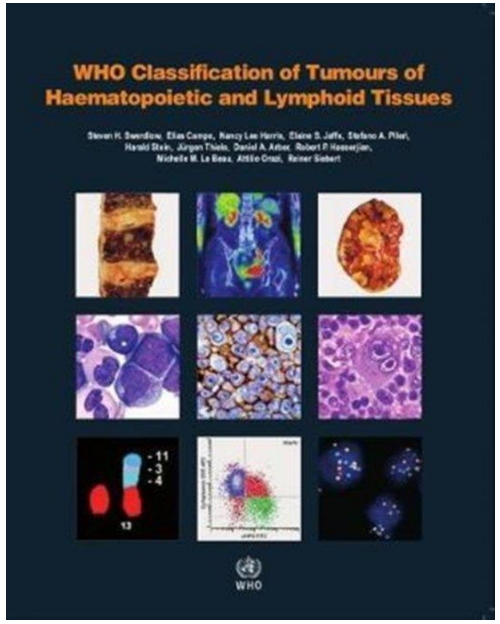
Table 6. 2022 ELN risk classification by genetics at initial diagnosis*

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]

Diagnosis and management of AML in adults..ELN: Blood sep 2022;140(12): 1345 ev

Classificatie acute leukemie

WHO 2016



REVIEW ARTICLE OPEN

Check for updates

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury[1], Eric Solary[2], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52]

The upcoming 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours is part of an effort to hierarchically catalogue human cancers arising in various organ systems within a single relational database. This paper summarizes the new WHO classification scheme for myeloid and histiocytic/dendritic neoplasms and provides an overview of the principles and rationale underpinning changes from the prior edition. The definition and diagnosis of disease types continues to be based on multiple clinicopathologic parameters, but with refinement of diagnostic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers. While a genetic basis for defining diseases is sought where possible, the classification strives to keep practical worldwide applicability in perspective. The result is an enhanced, contemporary, evidence-based classification of myeloid and histiocytic/dendritic neoplasms, rooted in molecular biology and an organizational structure that permits future scalability as new discoveries continue to inexorably inform future editions.

Leukemia; https://doi.org/10.1038/s41375-022-01613-1

Acute Myeloïde Leukemie: algemeen: definitie

- > 20% blasten in het beenmerg

  uitzondering:

  - AML met een specifieke genetische afwijking waarbij kliniek en beloop hetzelfde is bij blasten% < 20%
  - AML of MDS na chemo- of radiotherapie: deze vallen in de WHO 2022 onder de groep myeloïde neoplasmata post cytotoxische therapie (MN-pCT)

Je kijkt in aspiraat (% bij flowcytometrie: vaak niet representatief door bloedbijmenging) maar soms dry tap : Blastenpercentage in histologie : lastiger als CD34-

Definitie lymfatisch vs myeloid

- myeloperoxidase of Sudan black kleuring positief > 3%

  uitzondering:

  - Auerse staaf: geen MPO/SBB nodig

  - SBB en MPO negatief maar immunofenotypering wijst op:
  - AML met minimale differentiatie
  - Acute ongedifferentieerde leukemie (AUL)
  - monocytaire/monoblastaire leukemie
  - pure erythroïde leukemia
  - acute megakaryoblastaire leukemia
  - acute basofiele leukemia
  - blastair plasmacytoïd dendritische cel neoplasma

Andersom geredeneerd: lymfatische leukemie moet immunofenotypisch kenmerken hebben van een T of B lymfoblast

WHO 2022

- Acute myeloïde leukemie met definierende genetische afwijkingen
  - Hierbij dus geen 20% criterium alleen wel nog bij *BCR ABL1* en *CEBPA*

ICC: >10% bij deze categorie)

Tabel 1: Acute myeloide leukemie
Acute myeloide leukemie met definierende genetische afwijkingen:
Acute promyelocytenleukemie met *PML::RARA* fusie
Acute myeloide leukemie met *RUNX::RUNX1T1* fusie
Acute myeloide leukemie met *CBFB::MYH11* fusie
Acute myeloide leukemie met *DEK::NUP214* fusie
Acute myeloide leukemie met *RBM15::MRTFA* fusie
Acute myeloide leukemie met *BCR::ABL1* fusie
Acute myeloide leukemie met *KMT2A* herschikking
Acute myeloide leukemie met *MECOM* herschikking
Acute myeloide leukemie met *NUP98* herschikking
Acute myeloide leukemie met *NPM1* mutatie
Acute myeloide leukemie met *CEBPA* mutatie
Acute myeloide leukemie, myelodysplasie gerelateerd
Acute myeloide leukemie met andere gedefinieerde genetische veranderingen

Acute myeloïde leukemie gedefineerd door differentiatie

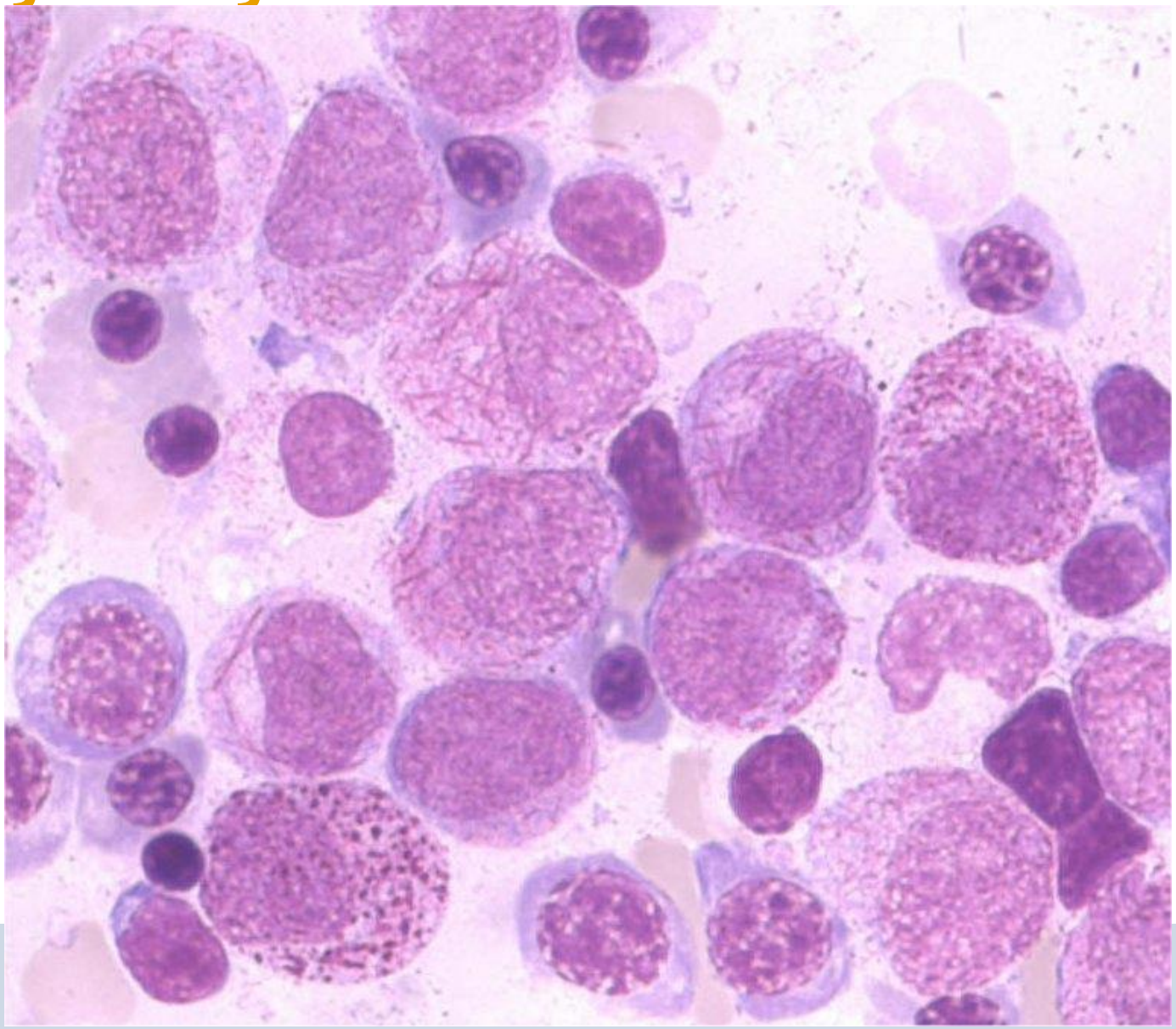
Acute myeloide leukemie gedefinieerd door differentiatie:
Acute myeloide leukemie met minimale differentiatie
Acute myeloide leukemie zonder maturatie
Acute myeloide leukemie met maturatie
Acute basofiele leukemie
Acute myelomonocytaire leukemie
Acute monocytaire leukemie
Acute erytroide leukemie
Acute megakaryoblastaire leukemie

AML t(15;17) (PML/RARα)
aka APL: acute promyelocyten leukemie

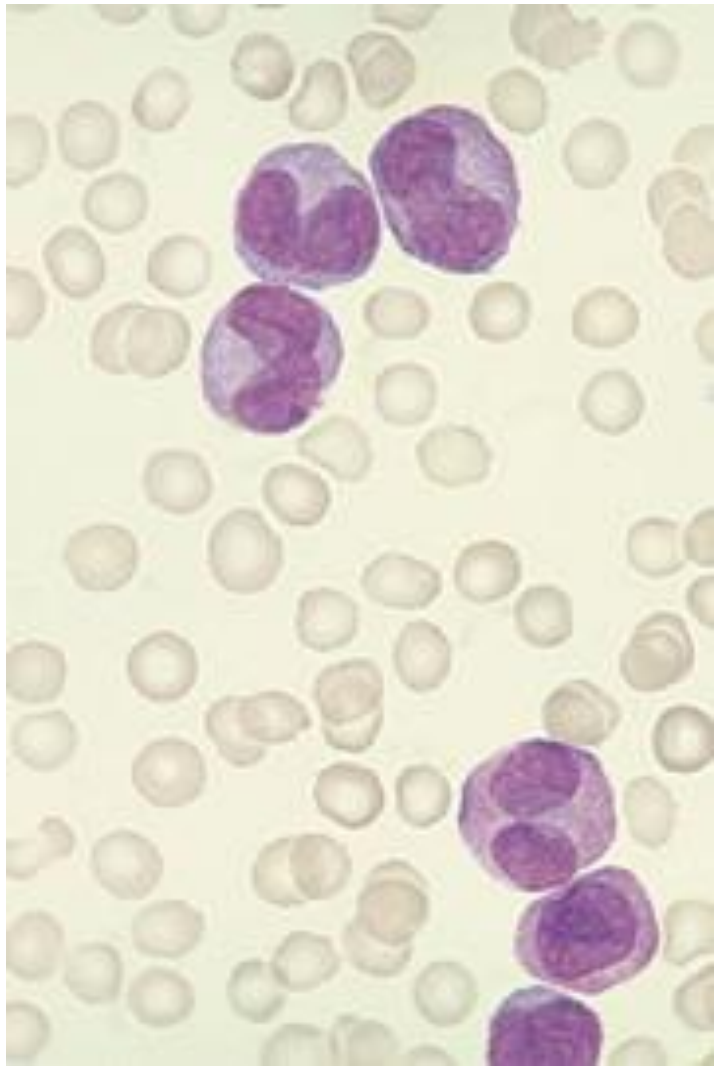
5-8% van AML
Meestel pancytopenie
diffuse intravasale stolling !
Dysplastische promyelocyt: takkenbos cellen, bilobaire nuclei, zeer veel granula
MPO sterk positief
My+ (CD33 homogeen, CD13 heterogeen), CD34-, HLADR-, CD15-
PML/RARα positief, meestal door t(15;17)

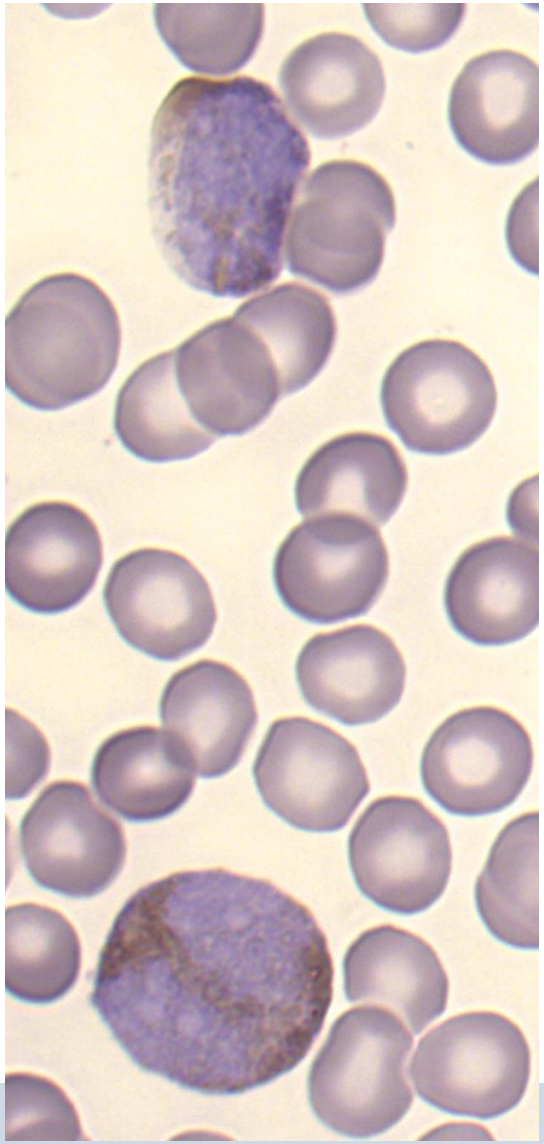
Microgranulair: leucocytose, bilobaire/vlindervormige kern, “leeg” cytoplasma
MPO: cytoplasma sterk +
CD34 deels+, CD2+

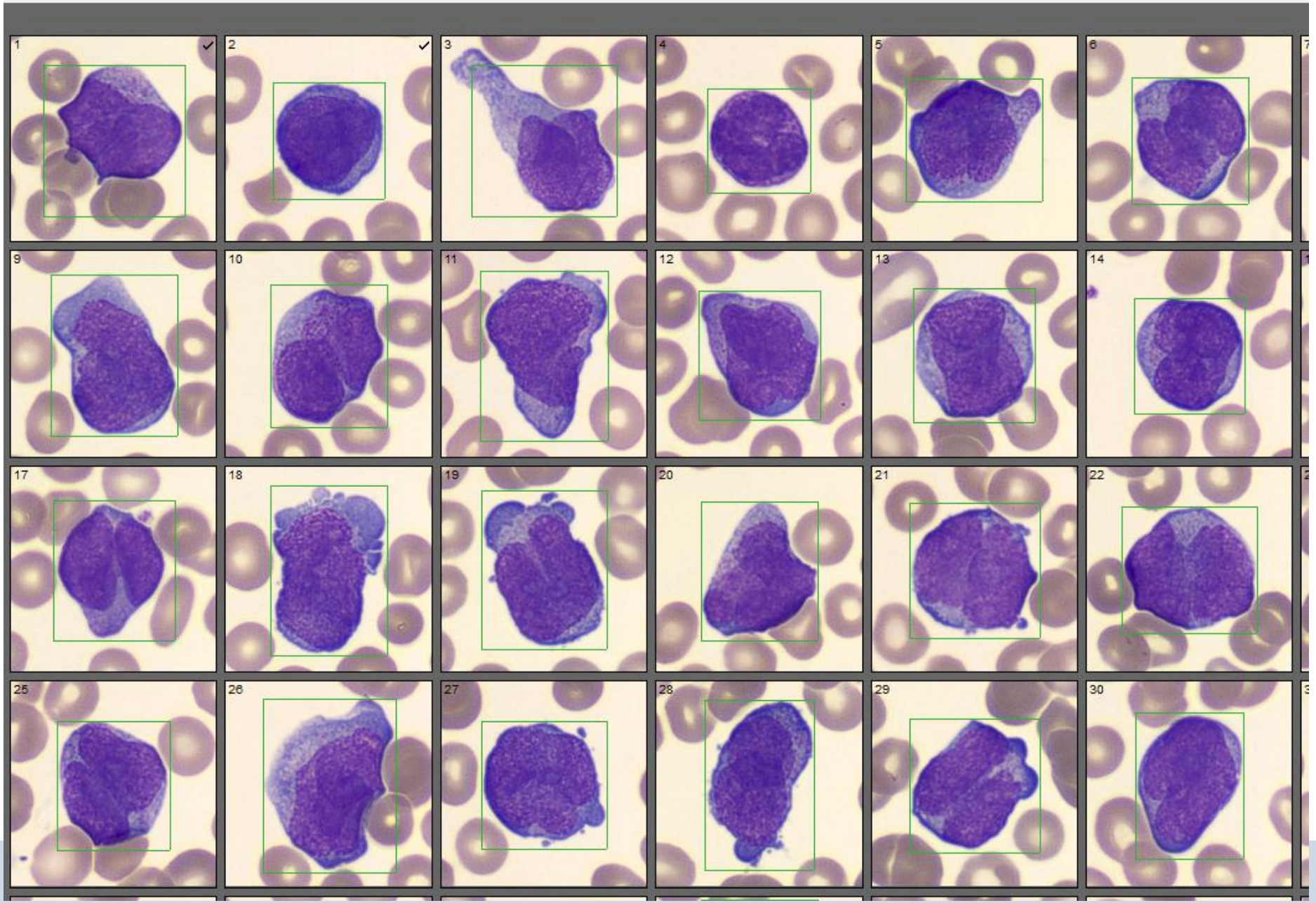
Acute promyelocyten leukemie



Variant APL



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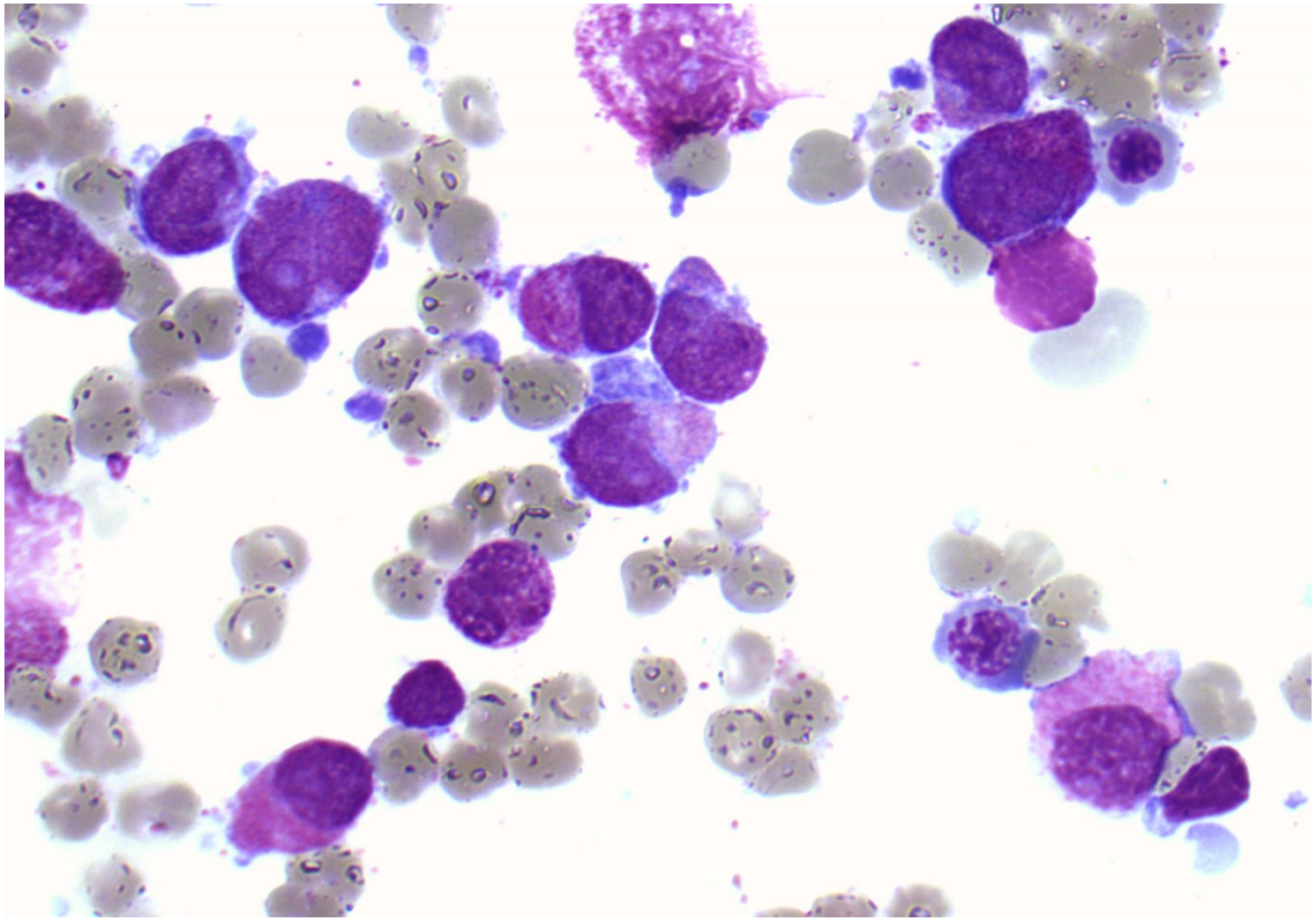

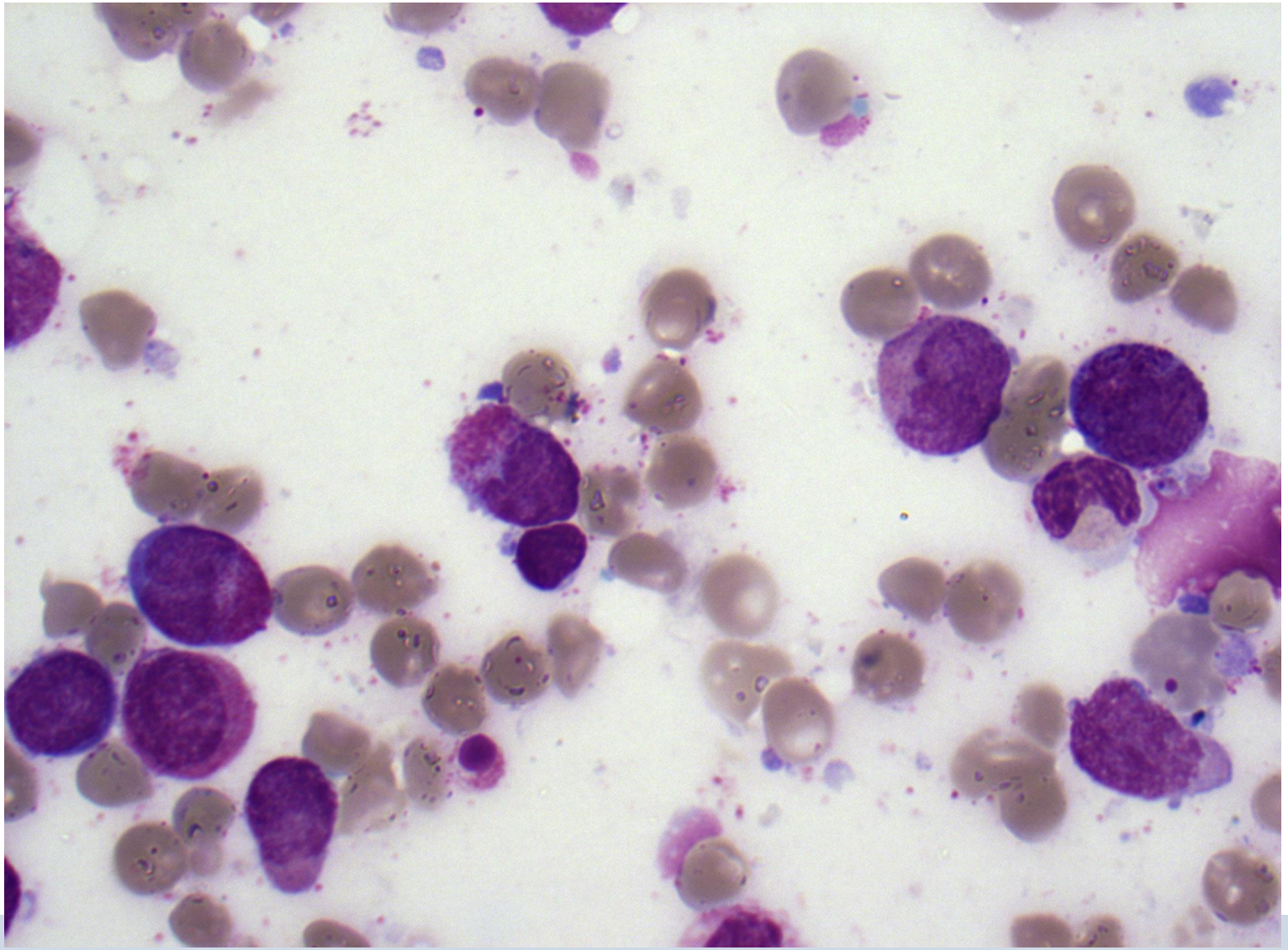

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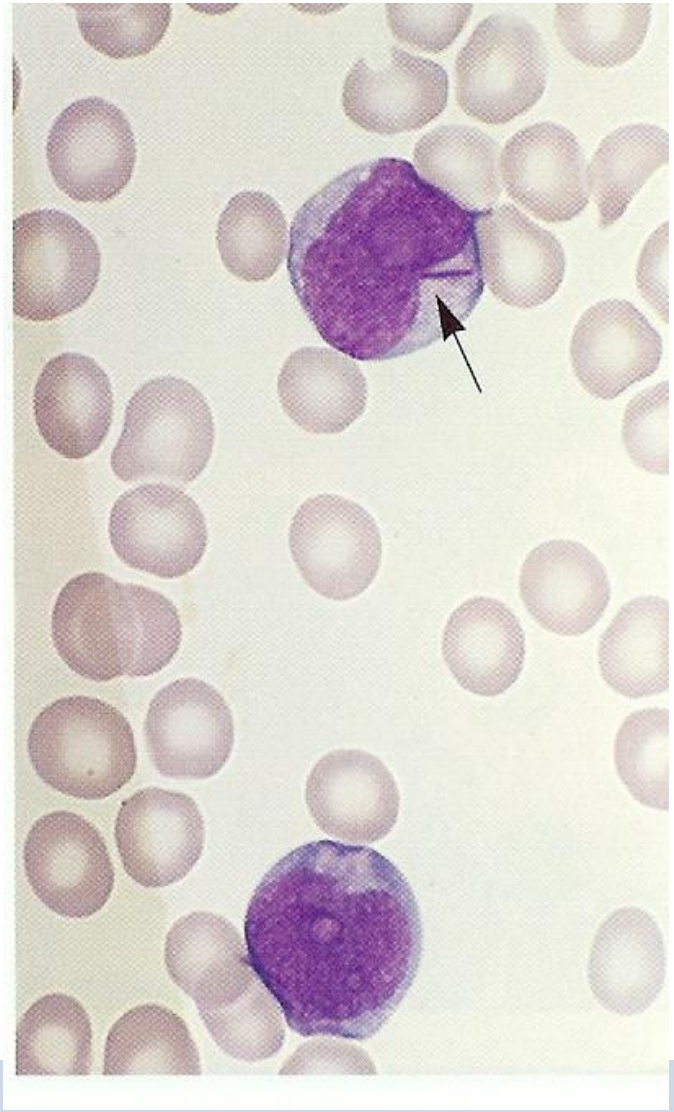
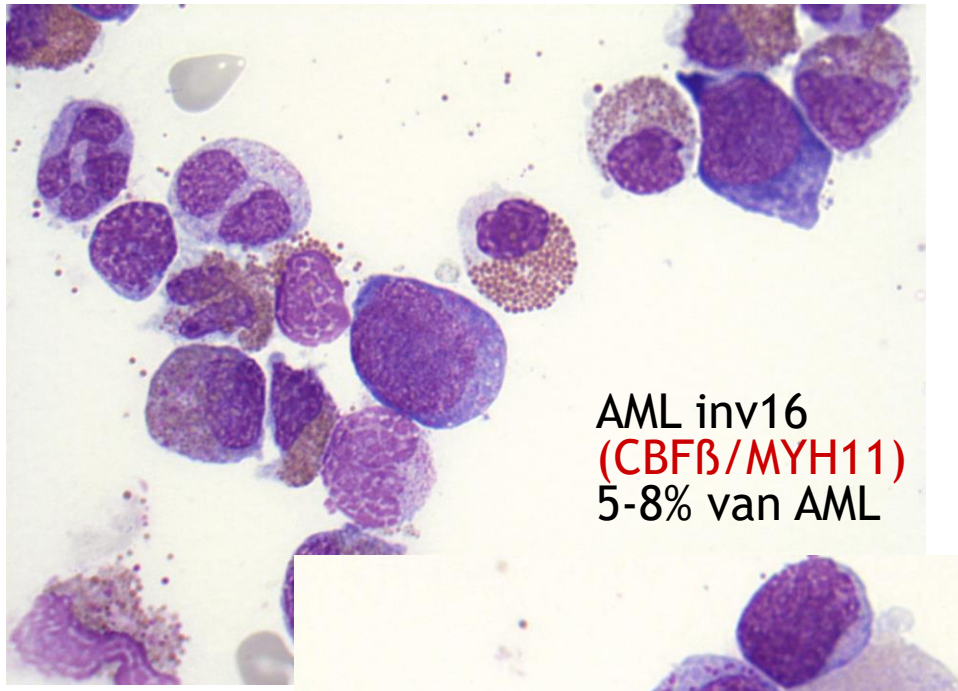


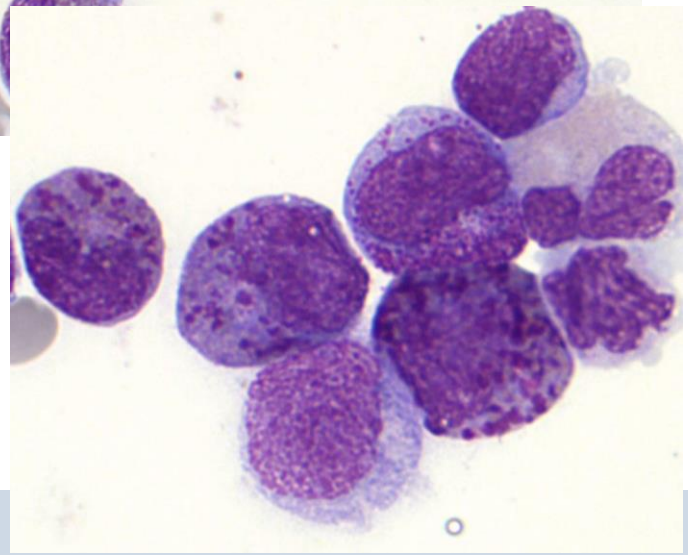
AML t(8;21) (AML/ETO)

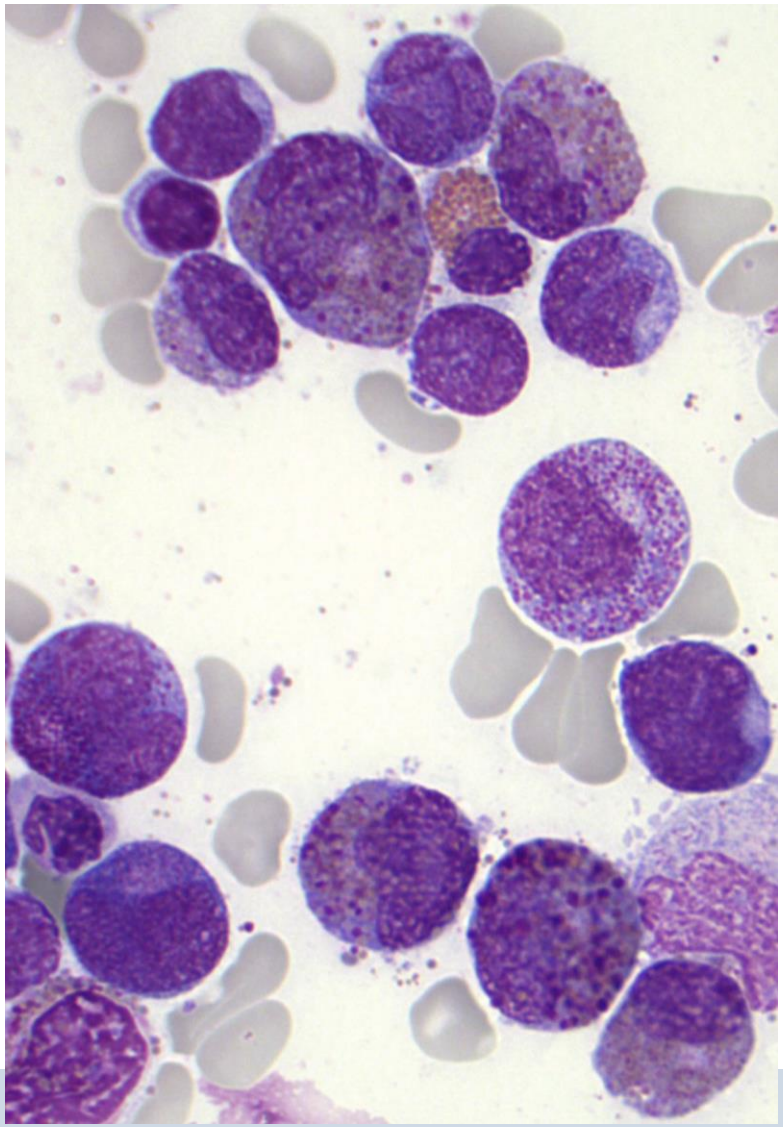
- dysgranulopoiese (abnormale segmentatie, grote granula, rozig cytoplasma)
- naaldvormige Auer staafjes (ook in granulocyten)
- sterke MPO/Sudan reactie
- CD19+ vaak
- 5% van AML

En dit?



AML inv16
(CBFß/MYH11)
5-8% van AML





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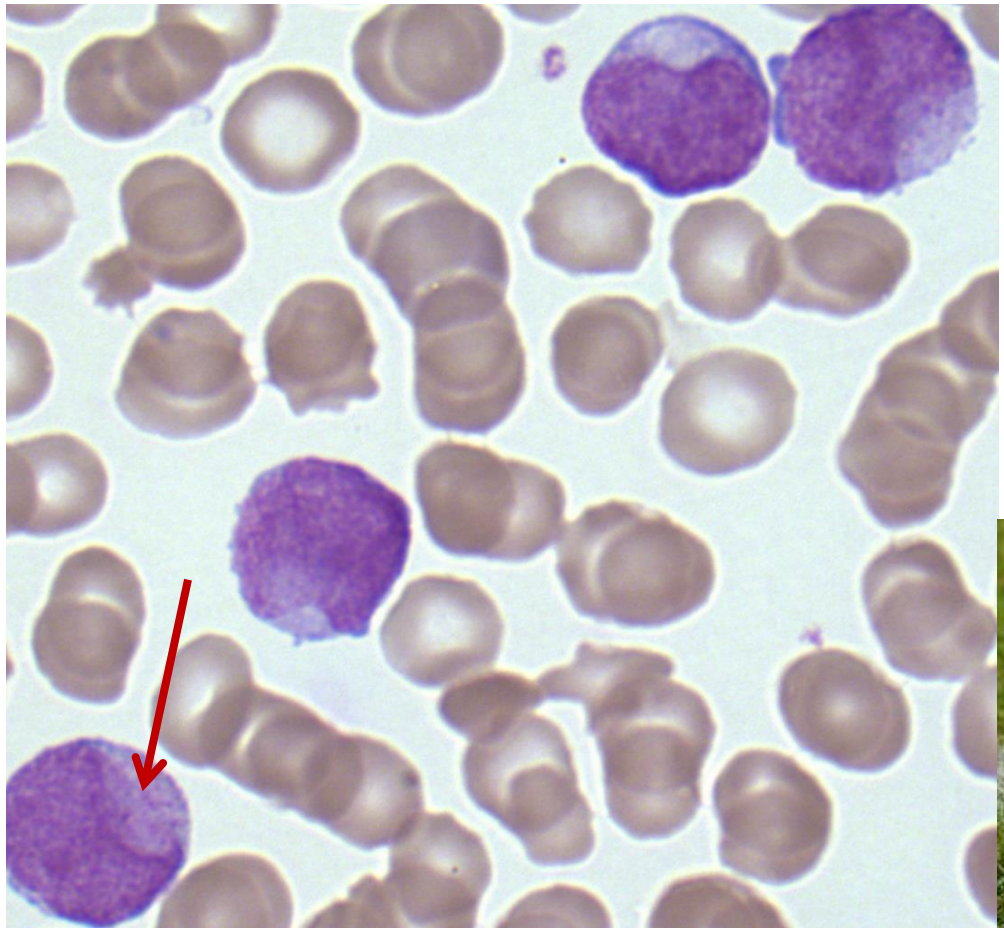
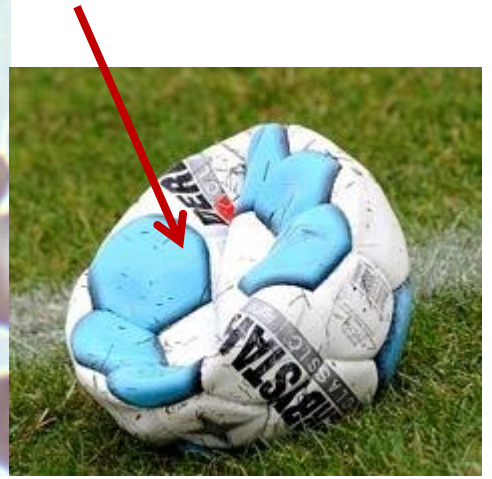




AML myelodysplasie gerelateerd

- ≥20% blasten, met MDS gerelateerde cytogenetische en/of moleculaire afwijkingen, de novo of na eerdere MDS/MPN

- Morfologische dysplasie is niet meer nodig voor diagnose
- Voorgeschiedenis met MDS

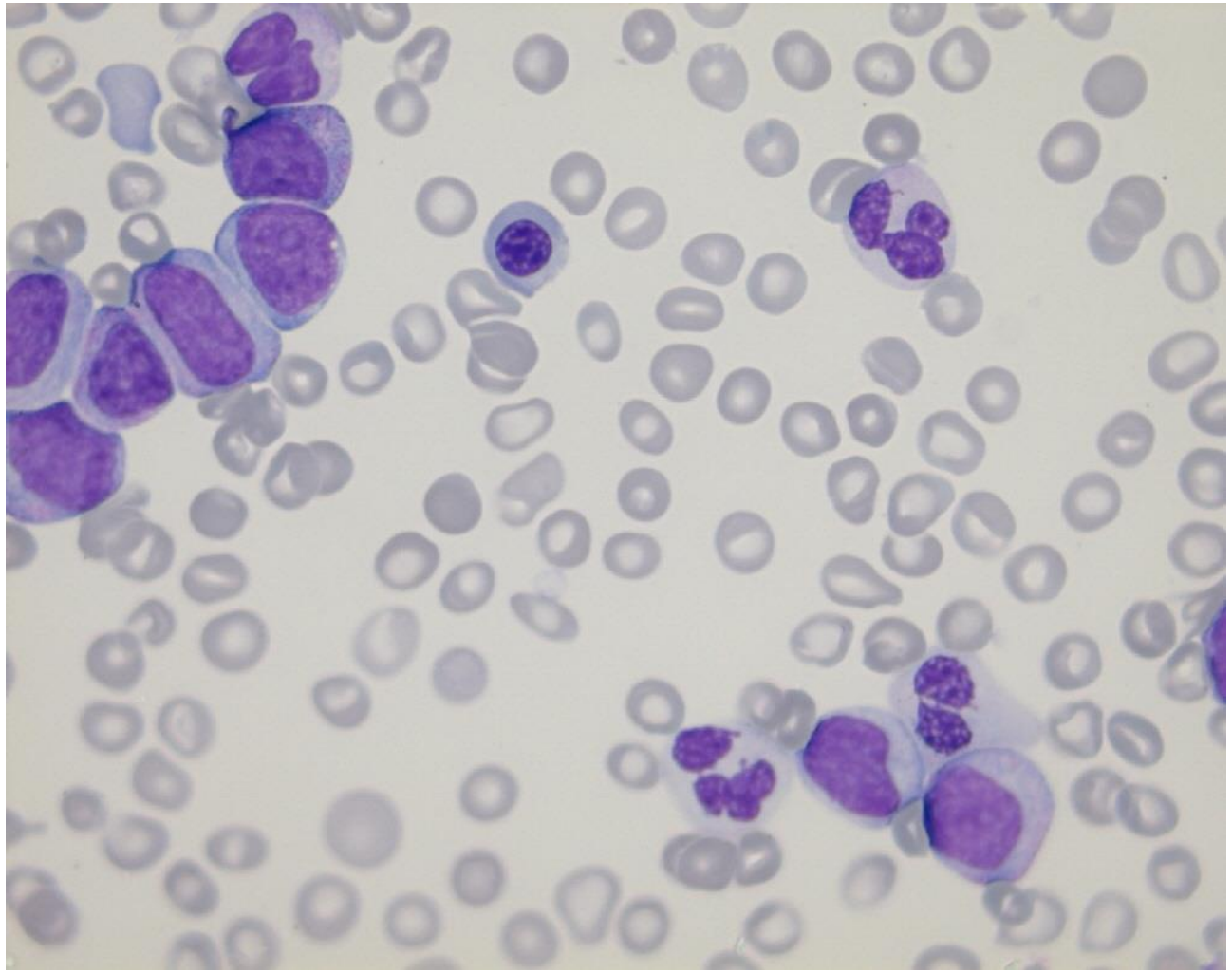
Nodig voor deze diagnose:

- de cytogenetische /moleculaire afwijkingen uit tabel
- En/of een voorgeschiedenis van MDS of MPN

Tabel 2. cytogenetische en moleculaire afwijkingen die *AML, myelodysplasie gerelateerd* definieren
Definierende cytogenetische afwijkingen:
Complex karyotype (≥3 afwijkingen)
5q deletie of verlies van 5q door ongebalanceerde translocatie
Monosomie 7 of 7q deletie of verlies van 7q door ongebalanceerde translocatie
11q deletie
12p deletie of verlies van 12p door ongebalanceerde translocatie
Monosomie 13 of 13q deletie
17p deletie of verlies van 17p door ongebalanceerde translocatie
Isochromosoom 17q
idic(X)(q13)
Definierende somatische mutaties:
ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

ICC ook runx1 mutatie, is weg uit WHO

AML met myelodysplasie gerelateerde veranderingen



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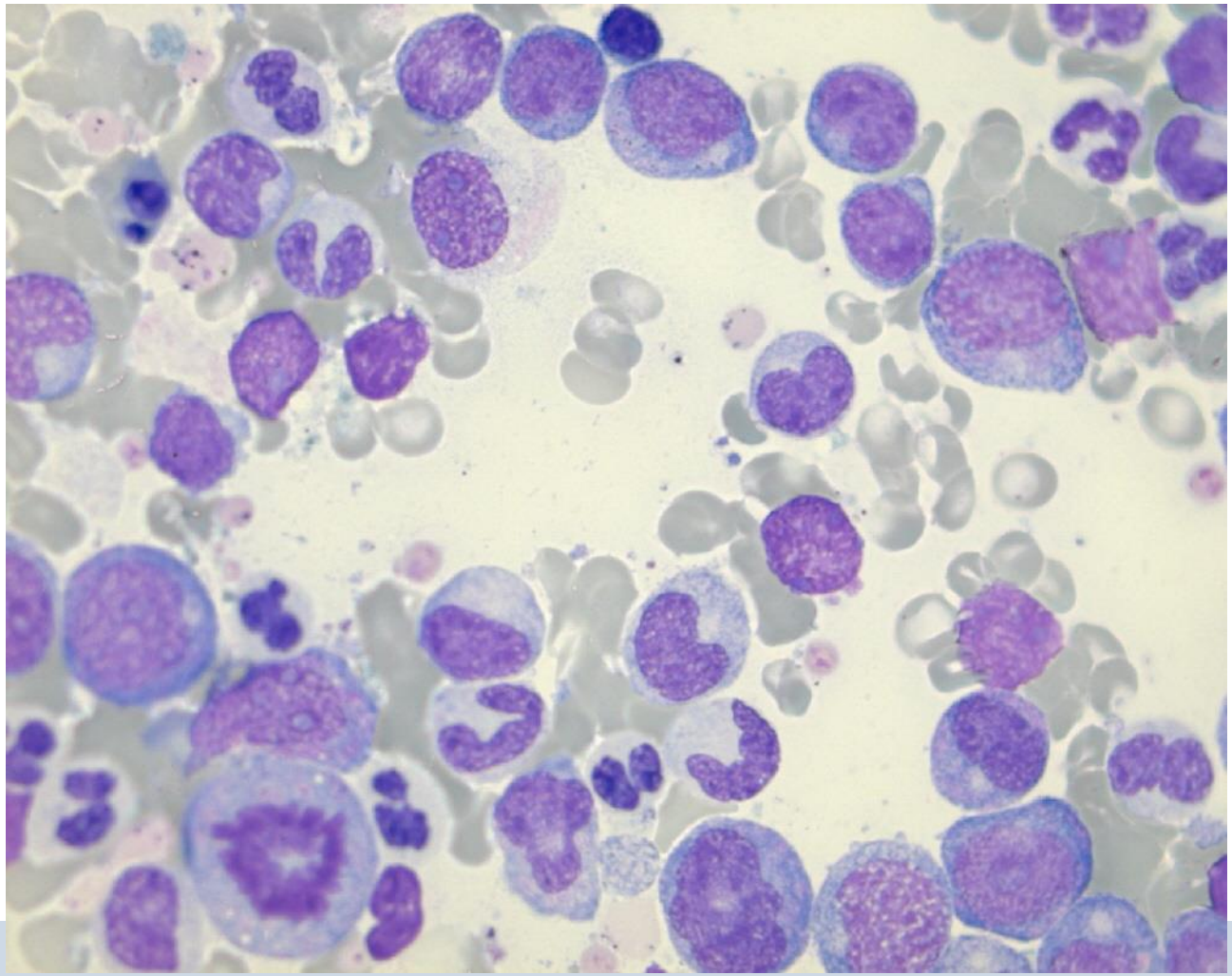
AML met myelodysplasie gerelateerde veranderingen

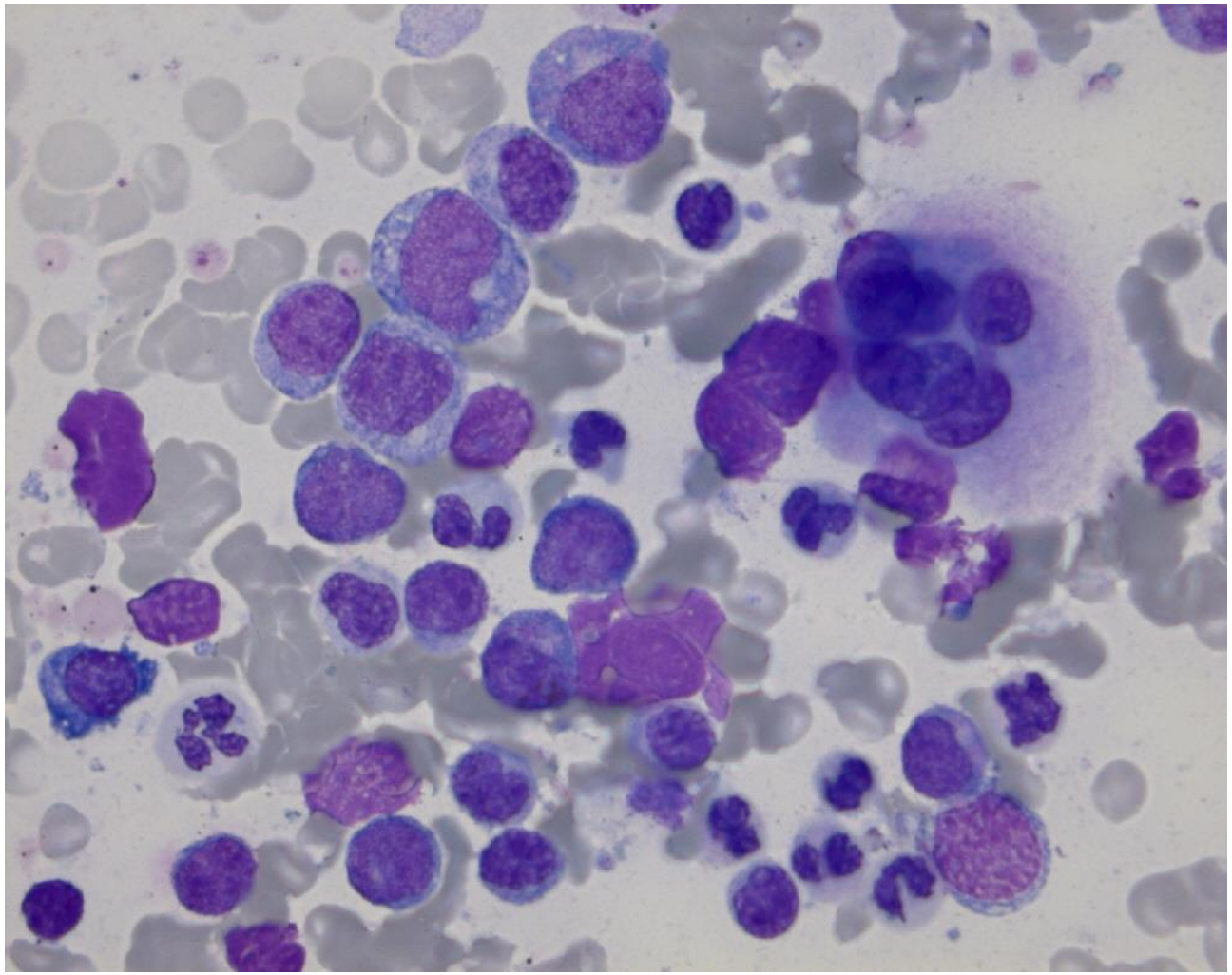


≥ 20% blasten

≥ 2 cellijnen ≥50% dysplasie

beenmerg

AML met myelodysplasie gerelateerde veranderingen



beenmerg

AML gedefinieerd door differentiatie

Tabel 3. Differentiatie kenmerken en criteria voor AML typen gedefinieerd door differentiatie

Omschrijving	kenmerken
AML met minimale differentiatie	MPO- of SBB-expressie van twee of meer van myeloid geassocieerde antigenen zoals CD13, CD33, CD117
AML zonder uitrijping	myeloïde uitrijping < 10%, ≥ 3% blasten positief voor MPO of SBB, expressie van twee of meer van myeloid geassocieerde antigenen zoals MPO, CD13, CD33, CD117
AML met uitrijping	myeloïde uitrijping > 10%, ≥ 3% blasten positief voor MPO of SBB, expressie van twee of meer van myeloid geassocieerde antigenen zoals MPO, CD13, CD33, CD117, < 20% van de cellen is monocytair
acute myelomonocytaire leukemie	monocytaire uitrijping ≥ 20%, myelocytaire uitrijping ≥ 20%, ≥ 3% blasten positief voor MPO
Acute monocytaire leukemie	Monoblasten, promonocyten en/of monocyten ≥ 80%, myelocytaire uitrijping <20%. Blasten en promonocyten hebben expressie van tenminste twee monocytaire markers zoals CD11c, CD14, CD36, CD64 of positiviteit voor NSE
Acute erytroïde leukemie	≥ 80% kernhoudende erytocytaire cellen met ≥ 30% proerytroblasten (< 80% kernhoudende erytrocytaire cellen sluit deze AML niet altijd uit)
acute megakaryoblasten leukemie	MPO- of SBB-expressie van een of meer van de markers CD41, CD42b, CD61
acute basofiele leukemie	Blasten en onrijpe basofielen met metachromasie bij toluidine blauw kleuring, blasten zijn negatief voor MPO, SBB en NSE en geen sterke CD117 expressie ter uitsluiting van mestcelleukemie

Myeloïd sarcoom

Tumor bestaand uit blasten met of zonder uitrijping, buiten het beenmerg
Architectuur oorspronkelijk weefsel is verwoest.
Kan ook met perifeer bloed betrokken en kan ook uit MDS/MPN ontstaan
Behandeld als AML
Soms aanvullende diagnostiek lastig

Secundaire myeloïde neoplasmata

- Post cytotoxische therapie
- Met kiemlijn predispositie

Myeloïde neoplasmata, secundair aan cytotoxische therapie (MN-pCT)

- t-AML, t-MDS and t-MDS-MPN
- Gedocumenteerde voorgeschiedenis van chemotherapie of groot veld radiotherapie
- Inclusief PARP remmers, exclusief mtx
- Zo precies mogelijk definieren dus indien van toepassing ook cytogenetische afwijking noemen en dan laten volgen door “post cytotoxische therapie”

10 - 20% van AML

- 5-6 jaar gemiddeld na alkylerende middelen, vaak met chromosoom 5, 7/complexe afwijkingen
- 2-3 jaar na topoisomerase remmers, translocaties met MLL

Myeloïde neoplasma met kiembaan predispositie

- AML, MDS en MDS/MPN in pt met genetische afwijkingen die geassocieerd zijn met myeloide maligniteiten

Table 10. Subtypes of myeloid neoplasms associated with germline predisposition.

Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction
• Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
• Germline *DDX41* P/LP variant[a]
• Germline *TP53* P/LP variant[a] (Li-Fraumeni syndrome)
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
• Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
• Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
• Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)
Myeloid neoplasms with germline predisposition and potential organ dysfunction
• Germline *GATA2* P/LP variant (GATA2-deficiency)
• Bone marrow failure syndromes
◦ Severe congenital neutropenia (SCN)
◦ Shwachman-Diamond syndrome (SDS)
◦ Fanconi anaemia (FA)
• Telomere biology disorders
• RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a,b])
• Down syndrome[a,b]
• Germline *SAMD9* P/LP variant (MIRAGE Syndrome)
• Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)[c]
• Biallelic germline *BLM* P/LP variant (Bloom syndrome)

[a]Lymphoid neoplasms can also occur.
[b]See respective sections.
[c]Ataxia is not always present.
P pathogenic, *LP* likely pathogenic.

WHO 2016

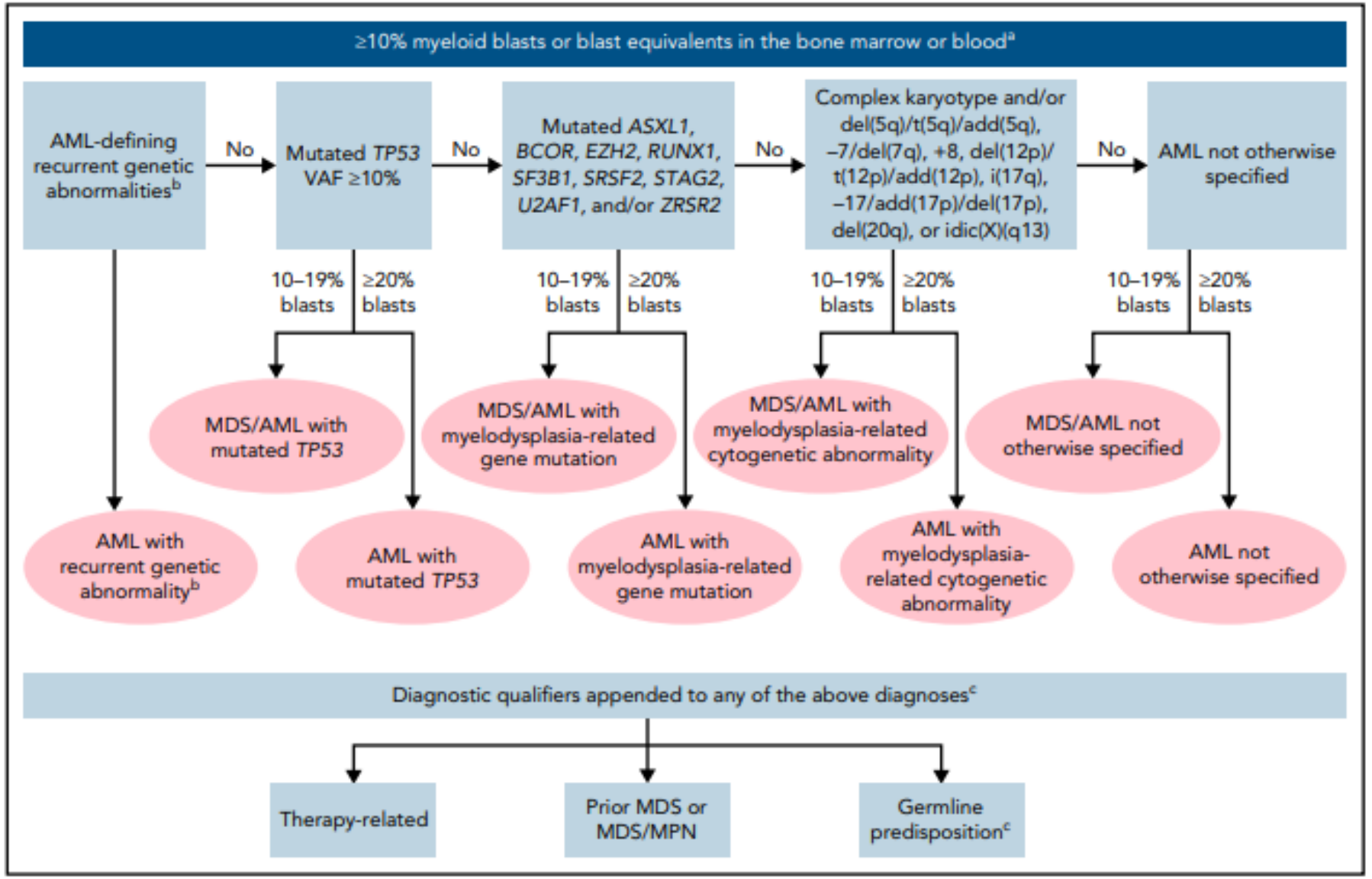
1. AML met specifieke (“recurrent”) cytogenetische afwijkingen
2. AML met myelodysplasie gerelateerde veranderingen
3. Myeloïde neoplasmata, therapie gerelateerd
4. AML niet anders te categoriseren (NOS)
5. Myeloïd sarcoom
6. Myeloïde proliferaties gerelateerd aan het syndroom van Down
7. Blastair plasmacytoïd dendritische cel neoplasma

WHO 2022

1. AML met definierende genetische afwijkingen
2. AML myelodysplasie gerelateerd
3. Myeloïde neoplasmata secundair aan cytotoxische therapie (MN-pCT)
4. AML gedefinieerd door differentiatie
5. Myeloïd sarcoom
6. Myeloïde neoplasma met kiembaan predispositie

secundair

ICC/ELN classification



Diagnosis and management of AML in adults..ELN: Blood sep 2022;140(12): 1345 ev

WHO 2022

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

ICC-MLN 2022

AML and related neoplasms
AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)[a]
• APL with t(15;17)(q24.1;q21.2)/*PML*::*RARA*[b]
• AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
• AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
• AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[c]
• AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214*
• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*[d]
• AML with other rare recurring translocations[e]
• AML with mutated *NPM1*
• AML with in-frame bZIP mutated *CEBPA*[f]
• AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*[a]
Categories designated AML (if ≥20% blasts in BM or PB) or MDS/AML (if 10-19% blasts in BM or PB)
• AML with mutated *TP53*[g]
• AML with myelodysplasia-related gene mutations Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
• AML with myelodysplasia-related cytogenetic abnormalities[h]
• AML not otherwise specified (NOS)

<u>Grootste verschillen:</u>

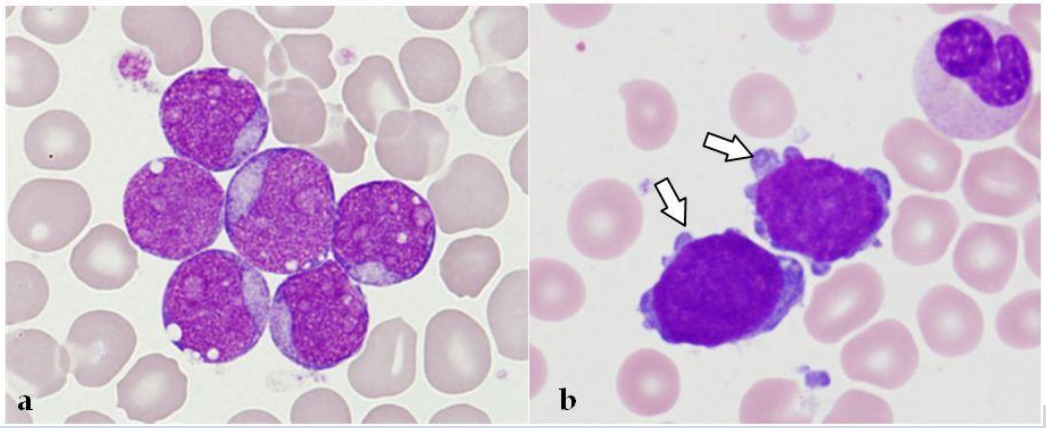
- Blastenpercentage en nomenclatuur AML vs. MDS/AML
- Waarde van TP53m in ICC-MLN
- biCEBPA + smbZIP vs. smbZIP only
- Definitie obv differentiatie vs. AML-NOS
- ELN-risicoclassificatie sluit goed aan bij ICC-MLN

Zeldzaam/gevorderden cursus

- AML met overige definierende genetische afwijkingen: voorlopige categorie
- Myeloide proliferaties gerelateerd aan Down syndroom
- ALAL/MPAL
- BPDCN

Myeloïde proliferaties gerelateerd aan het syndroom van Down

Voorbijgaande abnormale hematopoiese (TAM)
In 10% van pasgeborenen met Down syndroom
Morfologie en IF als van AML
Meest spontane remissie in eerste 3 maanden
1-3 jr later, 20-30% wordt AML
IF: MPO-, CD41 en CD61 +



ALAL (acute leukemia of ambiguous lineage) MPAL (mixed phenotype acute leukaemia)

met definierende genetische afwijkingen of immunofenotypisch gedefinieerd

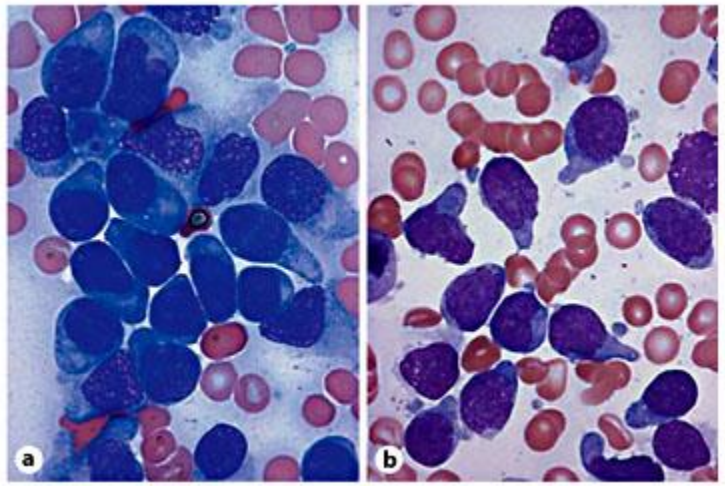
AUL

Acute ongedifferentieerde leukemie
Negatief voor myeloïde, B en T cel markers
Vaak positief voor blastenmarker CD34, tdt

Uitsluiten andere afkomst cellen door uitgebreid panel:
Cave plasmacytoid dendritische cel tumor, megakaryo, basofiel, NK-cel of solide tumor

WHO 2016: Acute Myeloïde Leukemie

2022 histiocytiare/dendritische cel neoplasmata

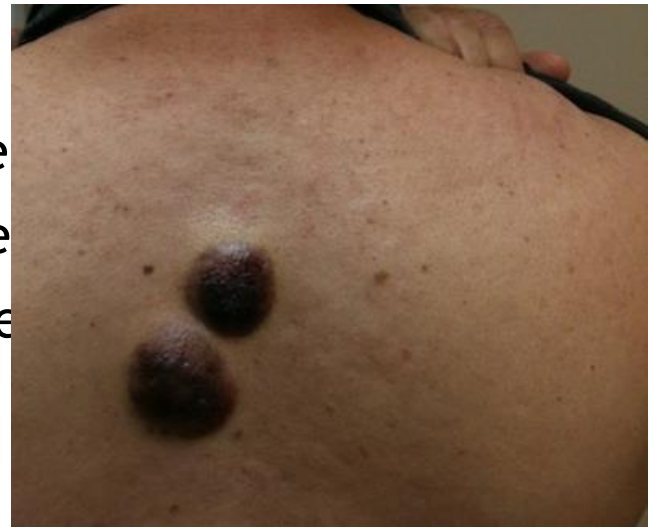


:urrent") cytoge

gerelateerde ve

herapie gerelate

oriseren (NOS)



- 6. Myeloïde proliferaties gerelateerd aan het syndroom van Down
- 7. Blastair plasmacytoïd dendritische cel neoplasma

- Diagnose mn IF: CD4, CD123, vaak CD56, CD68 in 50%. huidafwijkingen

Tijdspad diagnostiek

- Diagnose bij acute leukemie moet vaak snel gesteld
- Morfologie kan binnen 1 uur als nood
- Immunofenotypering kan binnen 1-2 dagen
- In theorie kan moleculaire diagnostiek en NGS dat ook maar in de praktijk is dat nog lang niet zo

- Nu heel veel definities obv cytogenetische /moleculaire afwijkingen
- Nu al wel voor enkele studies snelle moleculaire diagnostiek: HOVON 150-156

Rol van de morfoloog anno 2022

"So far, no one's seemed to notice."

2022 Tijd nodig: 1 uur

- Kwaliteit van sample
- Criteria voor diagnose (% blasten)
- ~~Criteria voor klassificatie (dysplasie)~~
- Aanvullend onderzoek sturen

Even oefenen

• blasten	28%
• promyelo’s	9%
• granulo’s	38%
• erythroid	17%
• dysplasie ery	>50%
• dysplasie meg	?
• dysplasie gran	>50%
• Auerse staafjes	+
• t(8;21)	+

<u>WHO</u>

-MDS IB2

-AML t(8;21)

-AML myelodysplasia gerelateerd

• blasten	28%
• promyelo’s	9%
• granulo’s	38%
• erythroid	17%
• dysplasie ery	>50%
• dysplasie meg	?
• dysplasie gran	>50%
• Auerse staafjes	+
• t(8;21)	+

WHO

-MDS IB2 (was EB-2)

-AML t(8;21)

-AML myelodysplasia gerelateerd

• blasten	18%
• promyelo’s	9%
• granulo’s	38%
• erythroid	27%
• dysplasie ery	>50%
• dysplasie meg	?
• dysplasie gran	> 50%
• Auerse staafjes	+
• t(8;21)	+

<u>WHO</u>

-MDS IB1

-MDS IB2 t(8;21)

-AML t(8;21)

-AML myelodysplasie gerelateerd

• blasten	18%
• promyelo’s	9%
• granulo’s	38%
• erythroid	27%
• dysplasie ery	>50%
• dysplasie meg	?
• dysplasie gran	> 50%
• Auerse staafjes	+
• t(8;21)	+

WHO

-MDS IB1 (was EB1)

-MDS IB2 t(8;21) (wasEB2)

-AML t(8;21)

-AML myelodysplasie gerelateerd

- blasten 65%
- promyelo’s 3%
- granulo’s 2%
- erythroid 30%
- dysplasie ery > 50%
- dysplasie meg -
- dysplasie gran < 50%
- Auerse staafjes +

<u>WHO</u>

-AML met minimale differentiatie
-AML zonder uitrijping
-AML MDS gerelateerd

• blasten	65%
• promyelo’s	3%
• granulo’s	2%
• erythroid	30%
• dysplasie ery	> 50%
• dysplasie meg	-
• dysplasie gran	< 50%
• Auerse staafjes	+

WHO

-AML met minimale differentiatie

-AML zonder uitrijping

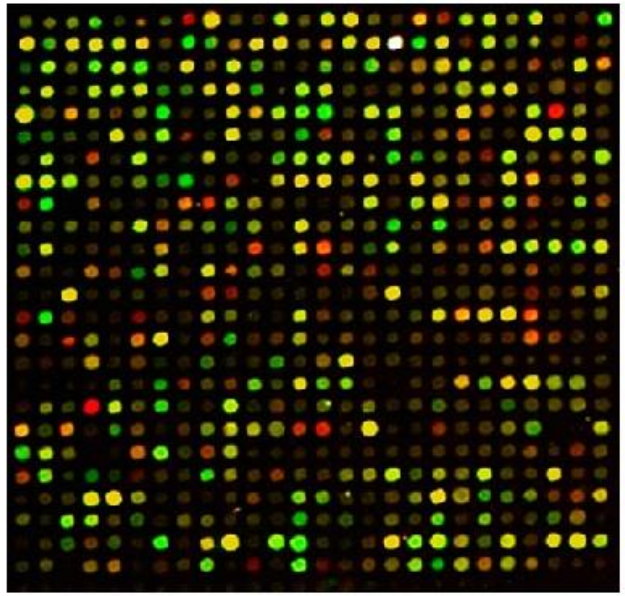
-AML MDS gerelateerd

Nagekomen bericht: NPM1 +

Wat nu?

Myelodysplasie

is morfologie nog wel nodig anno 2022 voor MDS diagnose?

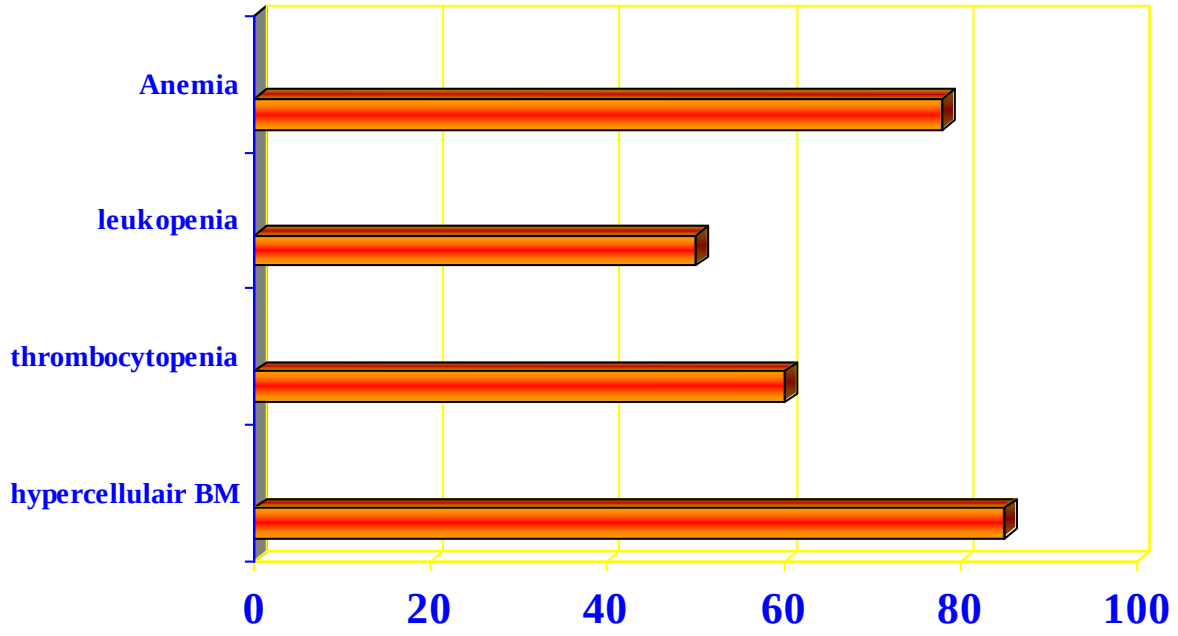


Microarray vs Next-generation sequencing

Je gaat het pas zien als je het doorhebt

J Cruijff

The paradox of peripheral cytopenia and hypercellular marrow



Laboratory findings at presentation

Met cytopenie

- maar geen dysplasie (<10%) en geen clonale markers: ICUS
- Geen dysplasie (<10%), wel clonale markers: CCUS

# of dysplasie

- Maar geen cytopenie en geen clonale markers: IDUS

Geen cytopenie en geen dysplasie en wel clonale markers: CHIP (meest 1 mutatie, lage VAF, DAT *DNMT3A, ASXLL1, TET2*

ICUS: idiopathic cytopenia of uncertain significance. IDUS: idiopathic dysplasia of unknown significance
CCUS: clonal cytopenia of uncertain significance
CHIP: clonal hematopoiesis of indeterminate potential

Diagnose MDS

Cytopenie (vaak milde macrocytose)

Dysplasie in 1 of meer cellijnen
(bloed, beenmerg cytologie/histologie)

Met of zonder clonale afwijkingen

Sluit andere ziekten uit

Diagnostische aanpak van MDS

Klinische data, beloop
Perifere diff
Compleet hemogram

Beenmergmorfologie-botbiopt
Cytogenetica, NGS (immuunfenotypering)
Serum folaat, vitamine B12, virologie

Diagnostiek van MDS

Diagnostic tool	Diagnostic value	Priority
Peripheral blood smear	Evaluation of dysplasia in one or more cell lineages Enumeration of blasts	Mandatory
Bone marrow aspirate	Dysplasia, blasts counts, ring sideroblasts	Mandatory
Bone marrow biopsy	Cellularity, CD34+ cells, fibrosis	Mandatory
Cytogenetic analysis	Allow a conclusive diagnosis, prognosis	Mandatory

Macovati et al, recommendations from the European LeukemiaNet, Blood, 2013, 122 (17):2943-2964

Diagnostiek van MDS

Diagnostic tool	Diagnostic value	Priority
FISH	Detection of targeted chromosomal abnormalities	Recommended
Flow cytometry immunophenotyping	Detection of abnormalities in cell lines, immature myeloid, maturing granulocytes, monocytes, immature and mature lymphoid compartments	Recommended
SNP array	Detection of chromosomal defects at a high resolution	Suggested
Mutation analysis of candidate genes	Detection of somatic mutations that can allow a conclusive diagnosis and prognostic evaluation	Recommended

Door experts, volgens guidelines, niet voor % blast

Macovati et al, recommandations from the European LeukemiaNet, Blood, 2013, 122 (17):2943-2964
Ook in: ESMO guidelines, Fenaux et al, Ann Oncol 2021

Dysplasie is niet specifiek voor MDS !

- deficienties (vit B12, foliumzuur)
- toxinen (arsenicum, benzeen, chemotherapie)
- congenitale dysplasie, PNH
- (virale) infecties (parvo B19, HIV)
- G-CSF
- opslag in anticoagulant > 2hr

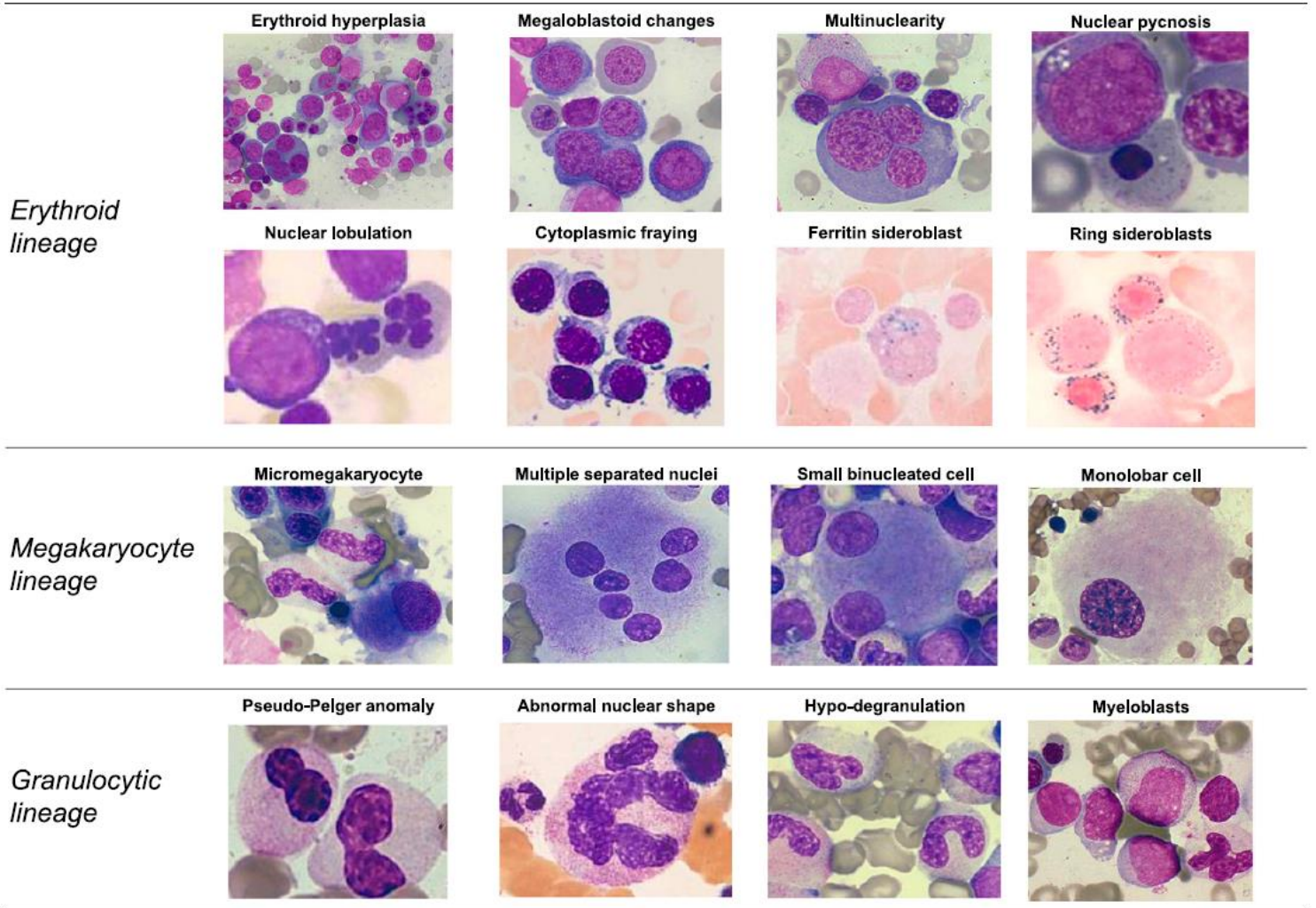


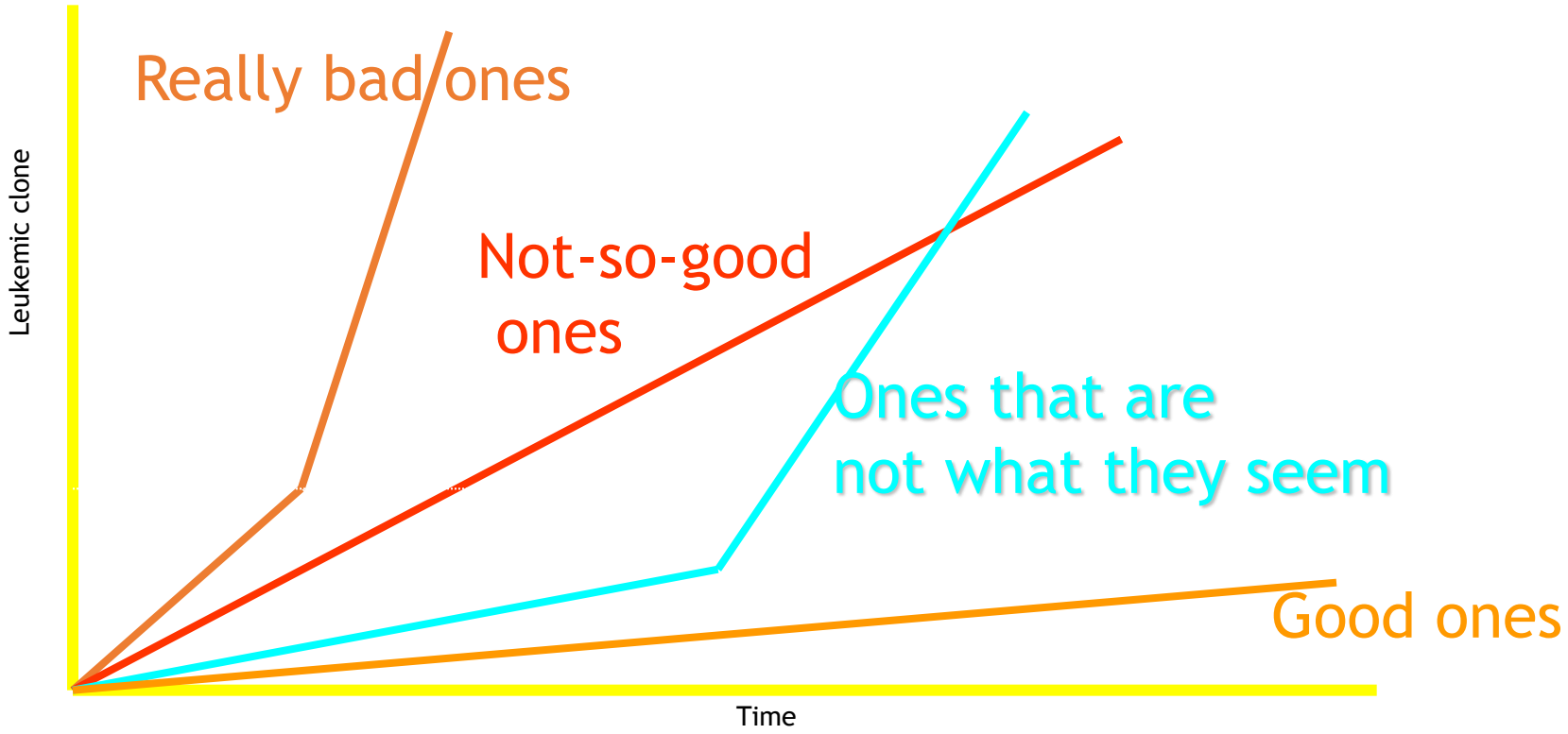
Figure 1. Representative examples of morphologic abnormalities of myelodysplasia. May Grünwald Giemsa staining in all cases with the only exception of ring sideroblasts (Perls staining). Magnification from 200× to 1000×, courtesy of Erica Travaglino.

Cazzola et al. Blood 2013;122:4021

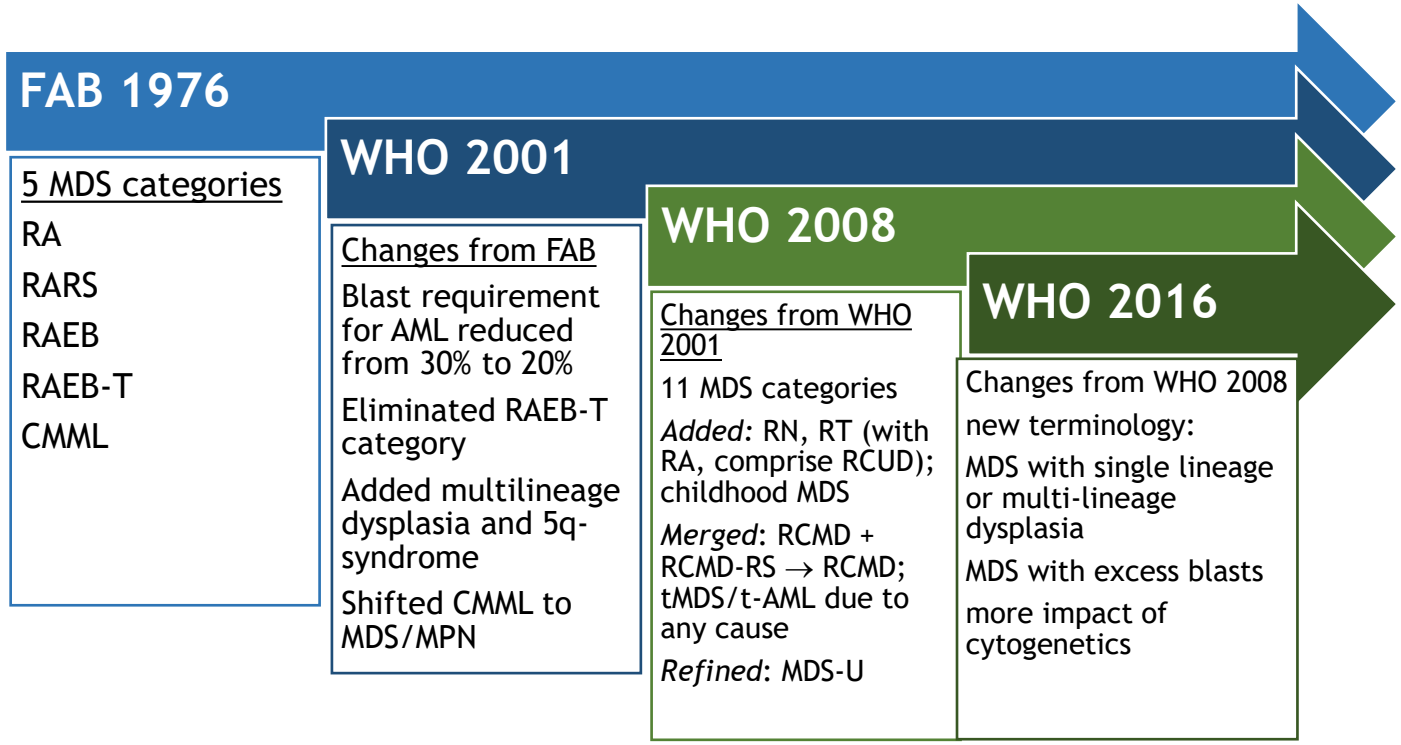
Andere diagnostische technieken

- Immuun fenotypering
- Cytogenetica (karyo, evt FISH als dit niet goed lukt)
- NGS voor al uw mutaties

Patterns of evolution of MDS



Eerder evolutie dan revolutie in MDS classificatie



En nu:
WHO 2022

RA, refractory anaemia; RARS, refractory anaemia with ringed sideroblasts; RAEB-)T), refractory anemia with excess blasts
(in transformation); RN, RT, refractory neturopenia/ thrombo-cytopenia; RCUD, refract. cytopenia with unilineage dysplasia; RCMD, with multilineage dysplasia; CMML, chronic myelo-monocytic leukemia; AML, acute myelogenous leukemia

Bennett JM, et al. Br J Haematol.1982;52:189-199.
Mufti GJ, et al. Haematologica 2008;93:1712-1717.
Garcia-Manero G, Hematol Am Soc Hematol Educ Prog. 2010;2010:330-337.
Haase D, et al. Blood. 2007;110:4385-4395.
Steensma DP, et al. Hematology Am Soc Hematol Educ Program 2009;645-655.
Vardiman JW, et al. Blood 2009:114:937-951

Arber et al,Blood 2016;127:2391.

WHO 2022

	blasten	
• MDS met definiërende cytogenetische afwijkingen		
• MDS met lage blasten en del5q	<5% in bm. <2%pb	Karyo/fish
• MDS met lage blasten en SF3B1 mutatie	<5% in bm. <2%pb	NGS
• MDS met biallelische TP53 inactivatie	<20% in bm en pb	NGS/FISH

	blasten
• MDS morfologisch gedefinieerd	
• MDS met lage blasten: MDS-LB	<5% in bm. <2%pb
• MDS hypoplastisch: MDS-h	<5% in bm. <2%pb
• MDS met toename van blasten:	
• MDS-IB1	5-9% bm of 2-4% pb
• MDS-IB2	10-19% bm of 5-19% pb of auerse staaf
• MDS met fibrose:MDS-f	5-19% bm 2-19% pb

en

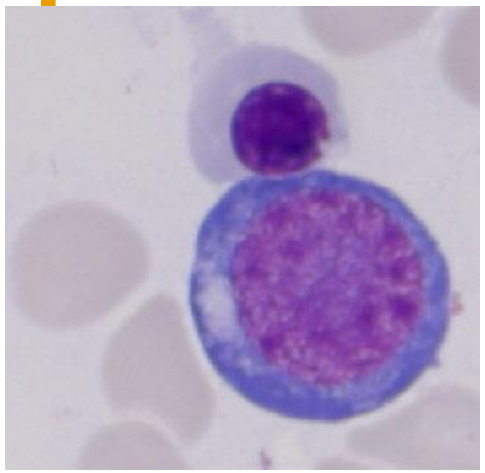
- Als je geen SF3B1 hebt en wel >15% ringsideroblasten: MDS-LB met RS
- Dysplasie is als 10% of meer van cellijn dysplastische kenmerken heeft
- Biallelisch TP53: met NGS VAF>50% of meerdere mutaties is zeer suggestief, >90% met complex/monosomaal karyotype
- Ook nieuw: MDS-h: overlap AA, immuun genese? , deel doet het op ATG en CSA

- ICC: heeft nog wel SLD en MLD, >10% blast heet MDS/AML, heeft geen MDS-h en MDS-f

Dysplasie erytropoiese

- Erytropoiese
  - megaloblastoid, karyorhexis, nucleaire fragmenten, multinucleatie
  - Ring-sideroblasten
  - Cytoplasmatische vacuoles, PAS positiviteit
- Granulopoiese
  - hypogranulatie
  - hyposegmentatie (pseudo Pelger-Huet anomalie)
  - bizarre gesegmenteerde kernen
- Megakaryopoiese
  - micromegakaryocyten
  - monogelobuleerde of meerdere losliggende kernen

dysplasie erytropoiese megaloblastoid



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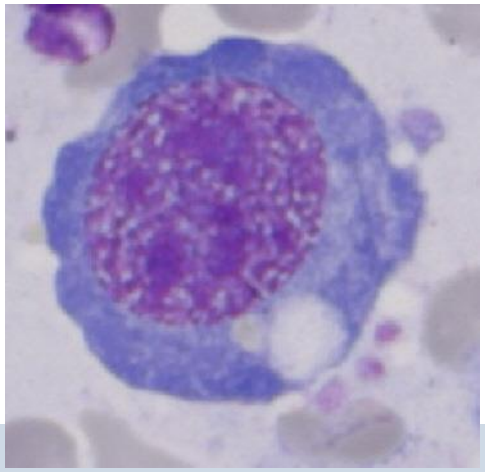
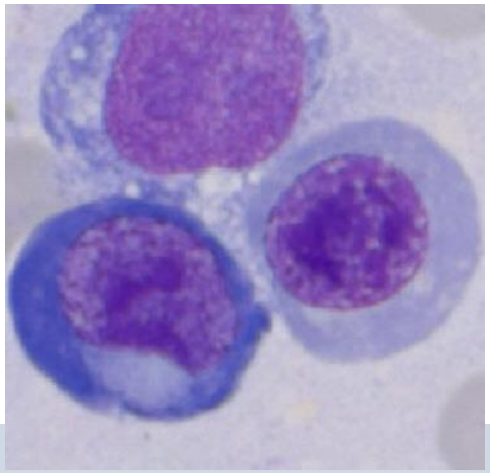
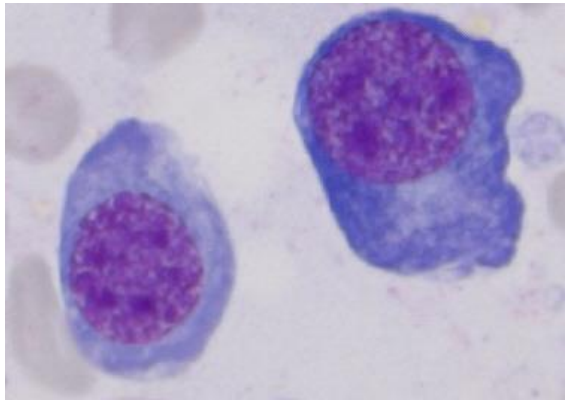
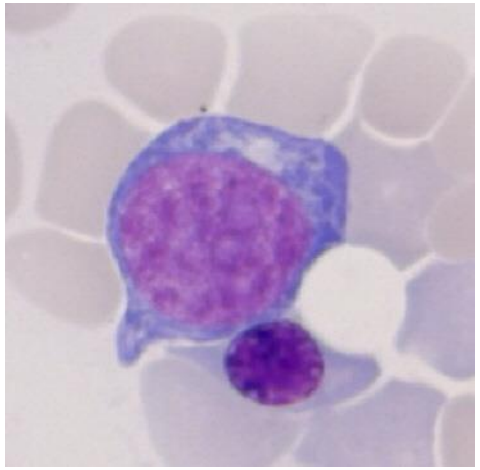






megaloblastoid

dysplasie erytropoiese
kernfragmentatie, abnormale kernen



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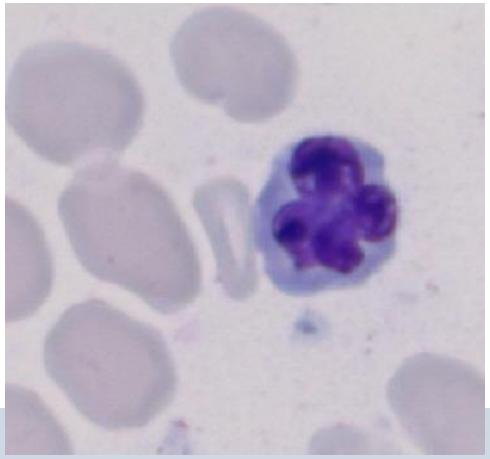
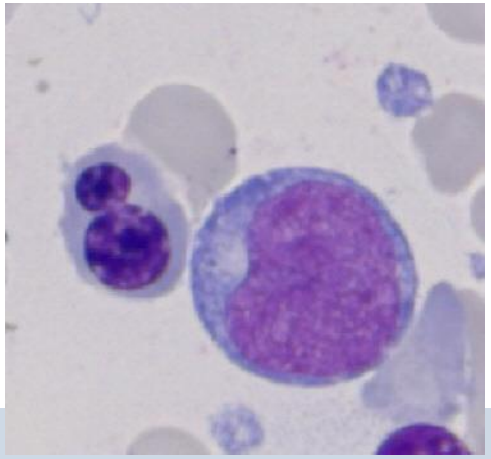
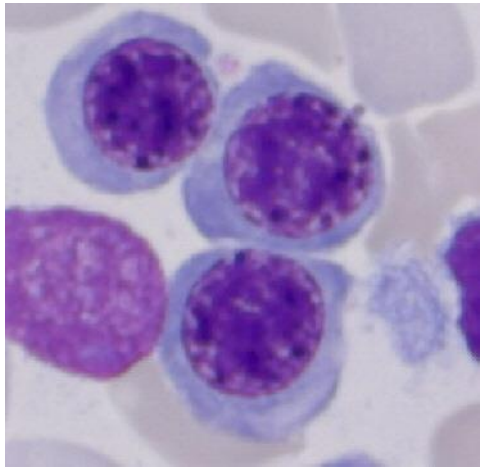




kernfragm, abn kernen

dysplasie erytropoiese meerkernigen



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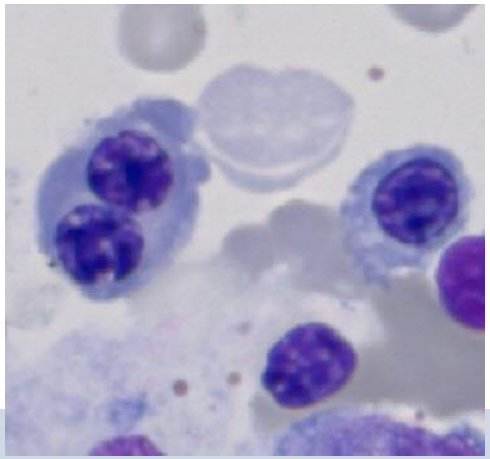
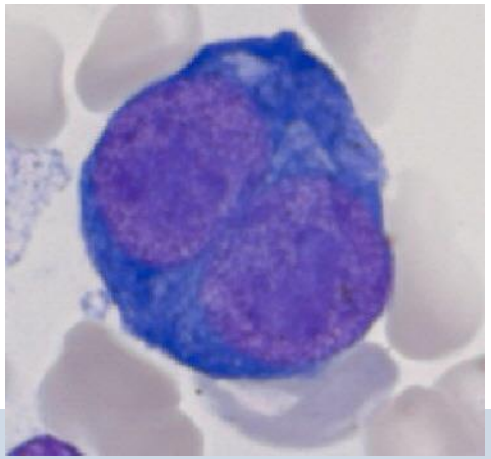
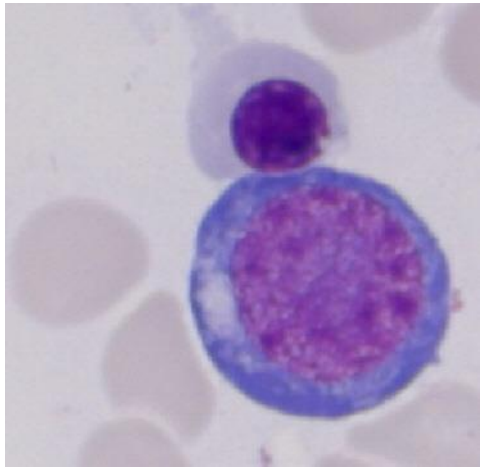




meerkernigen

dysplasie erytropoiese vacuolisatie



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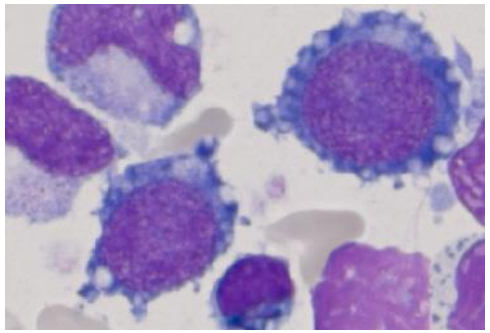
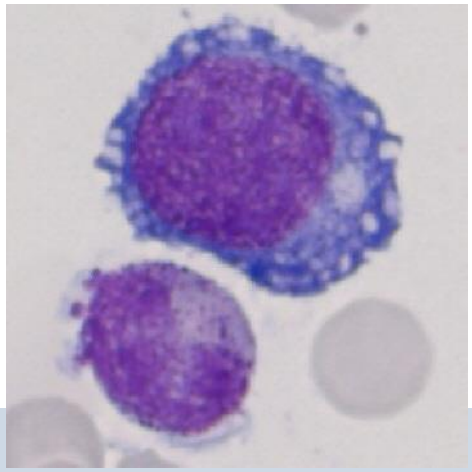
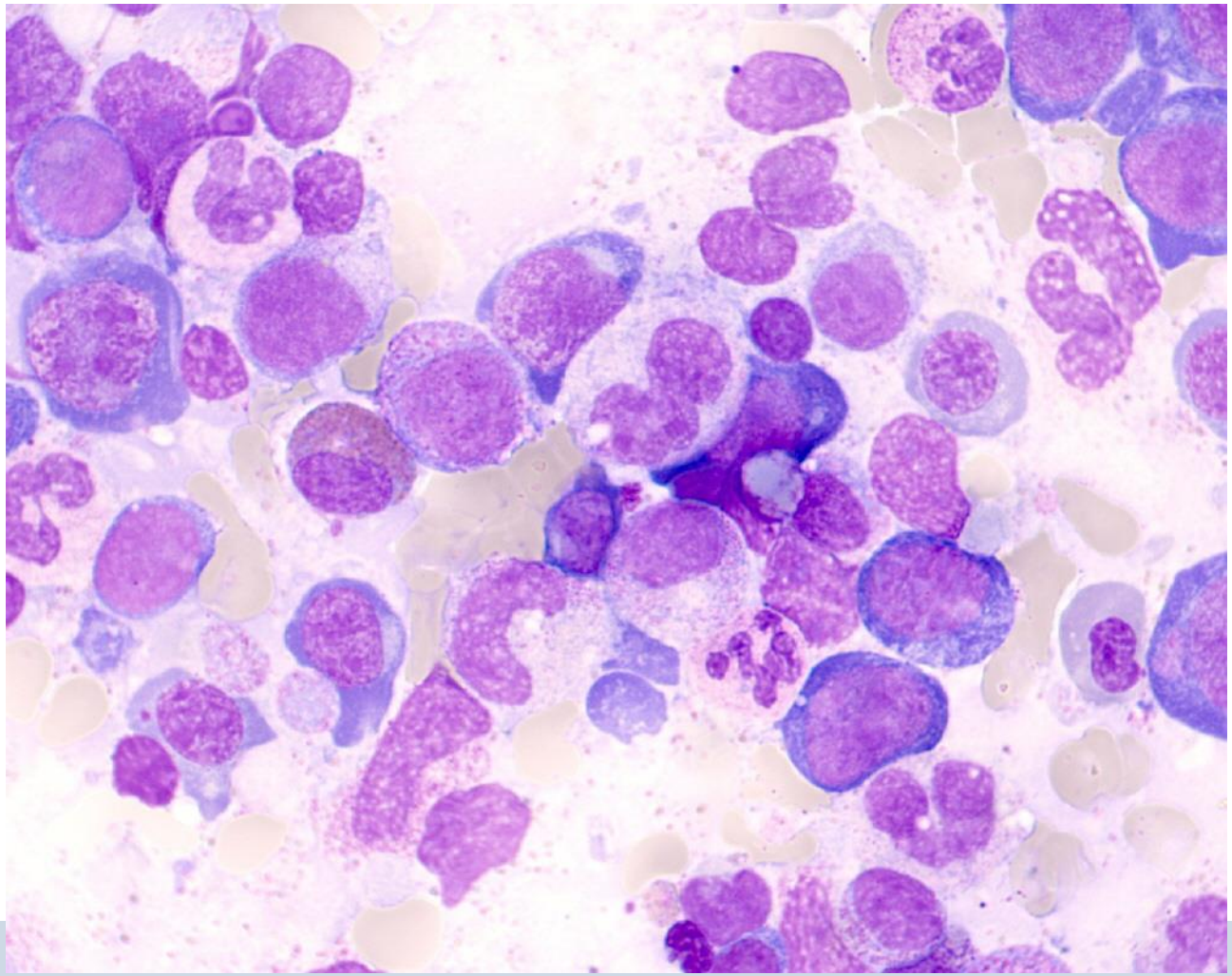




vacuolisatie

dysplasie erytropoiese



-megaloblastoid

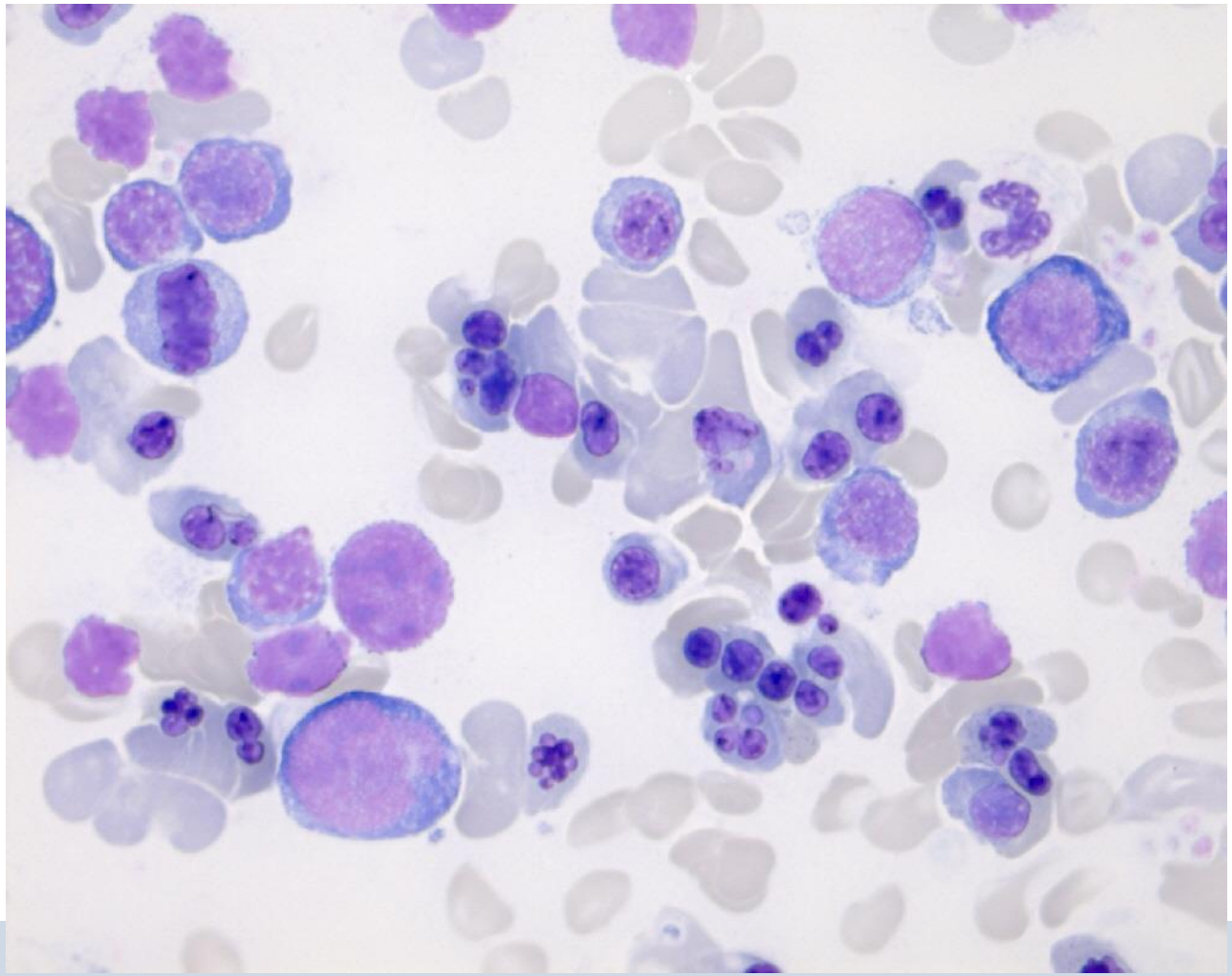
-abnormale kernen

-kernfragmentatie

-vacuolisatie

beenmerg

dysplasie erytropoiese



-megaloblastoid

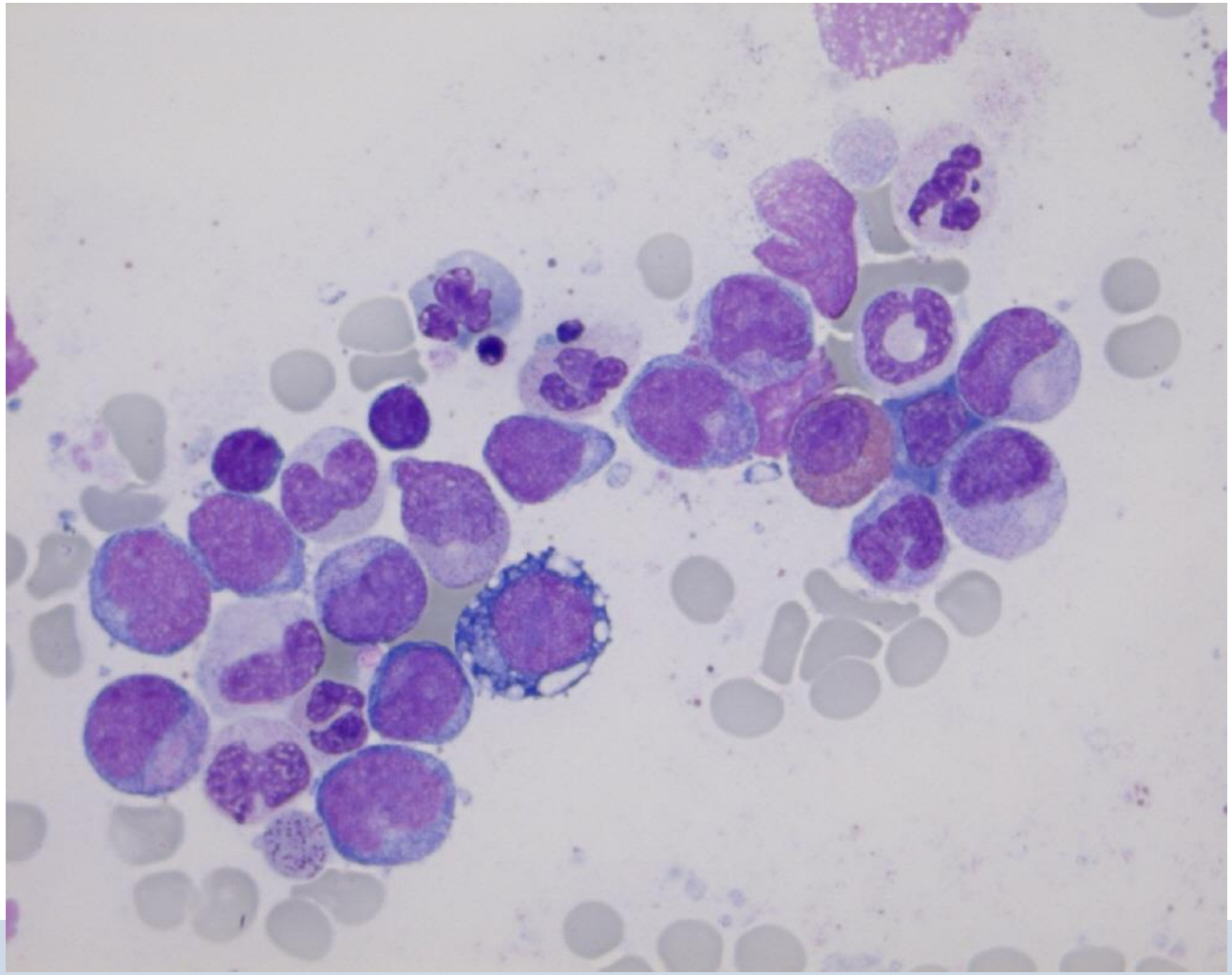
-abnormale kernen

-kernfragmentatie

-vacuolisatie

beenmerg

dysplasie erytropoiese



-megaloblastoid

-abnormale kernen

-kernfragmentatie

-vacuolisatie

beenmerg

Dysplasie granulopoiese

- Erytropoiese
  - megaloblastoid, karyorhexis, nucleaire fragmenten, multinucleatie
  - Ring-sideroblasten
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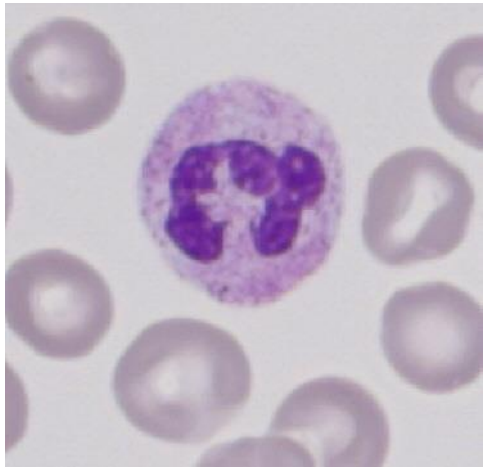
  - hyposegmentatie (pseudo Pelger-Huet anomalie)
  - bizarre gesegmenteerde kernen
- Megakaryopoiese
  - micromegakaryocyten
  - monogelobuleerde of meerdere losliggende kernen

dysplasie granulopoiese pseudo Pelger-Huet



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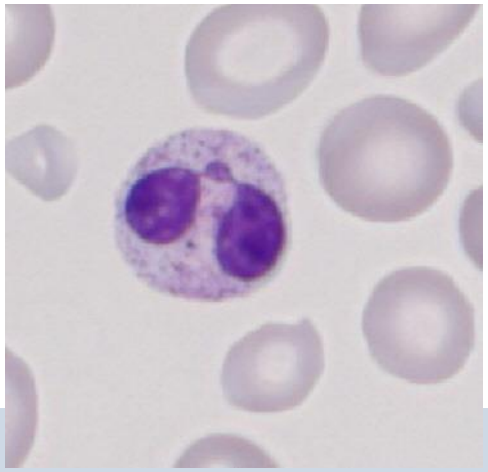
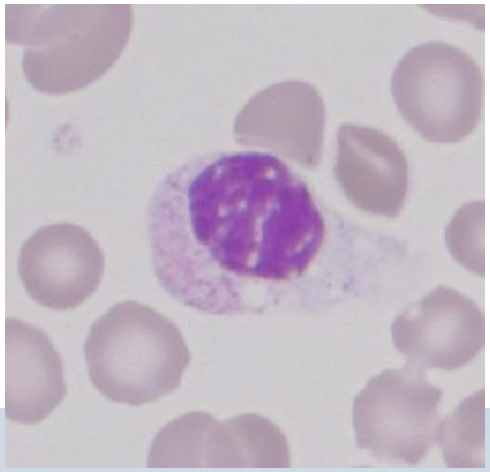
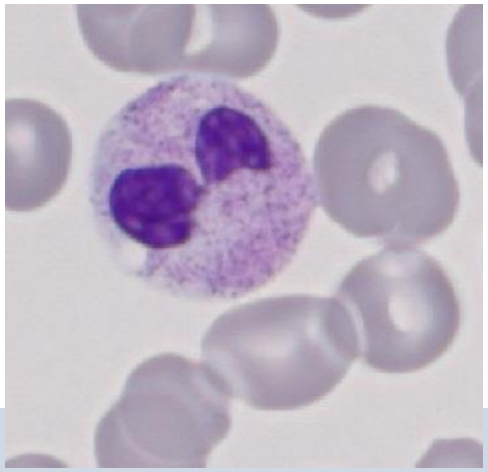
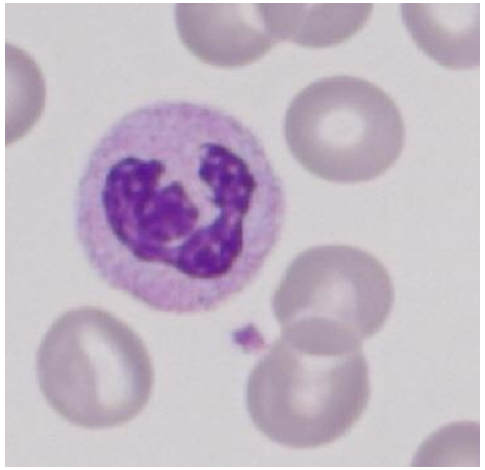






Pseudo Pelger-Huet

dysplasie granulopoiese
hypogranulatie



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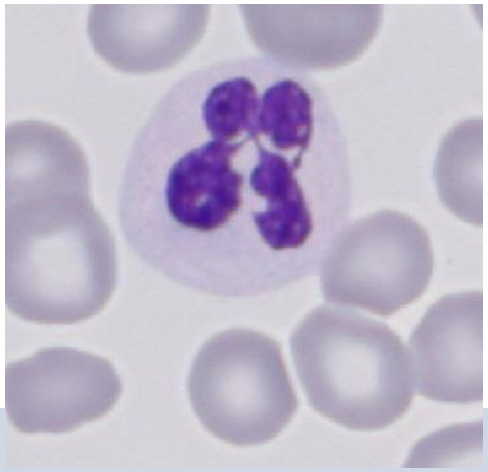
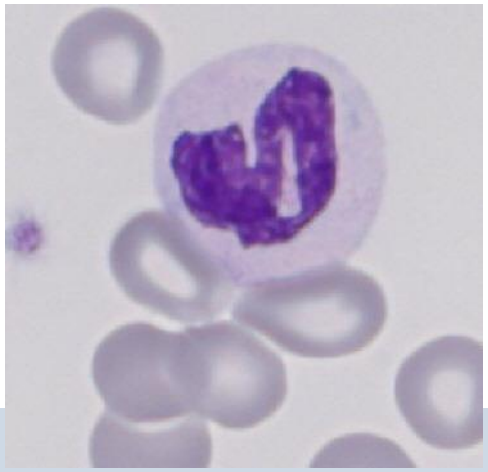
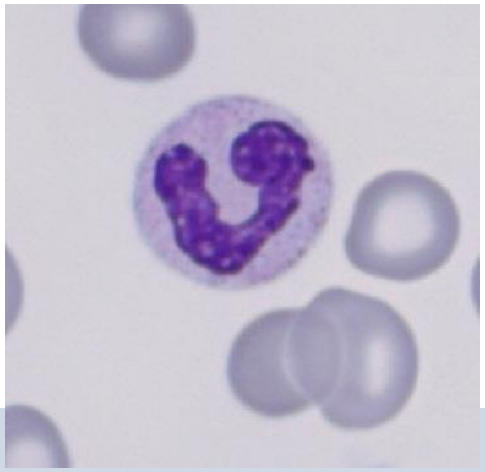
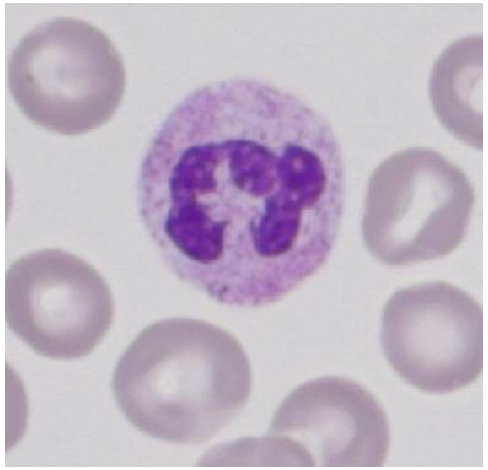




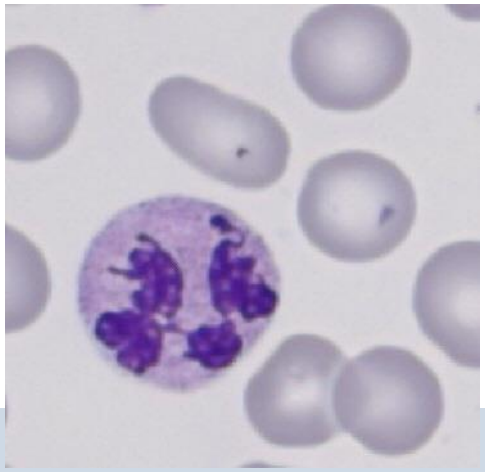


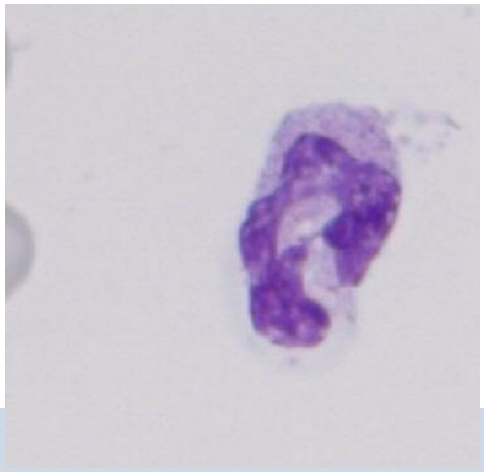
hypogranulatie

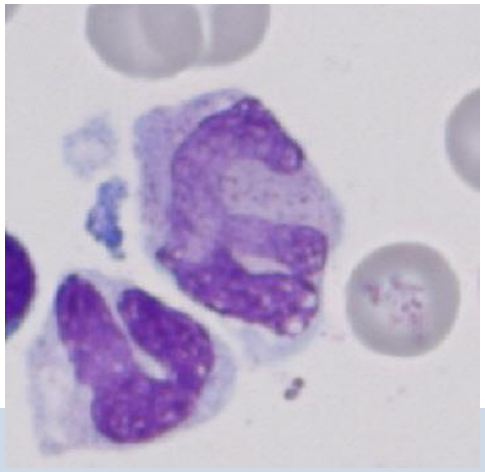
dysplasie granulopoiese
bizarre vormen



normaal

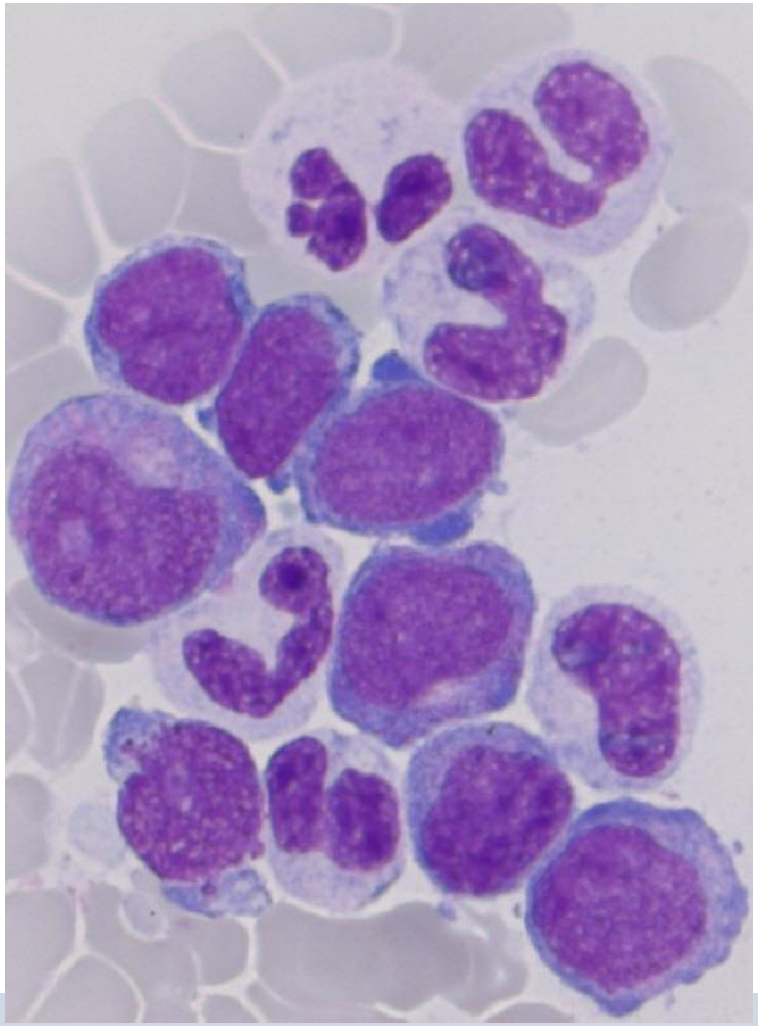






bizarre vormen

dysplasie granulopoiese

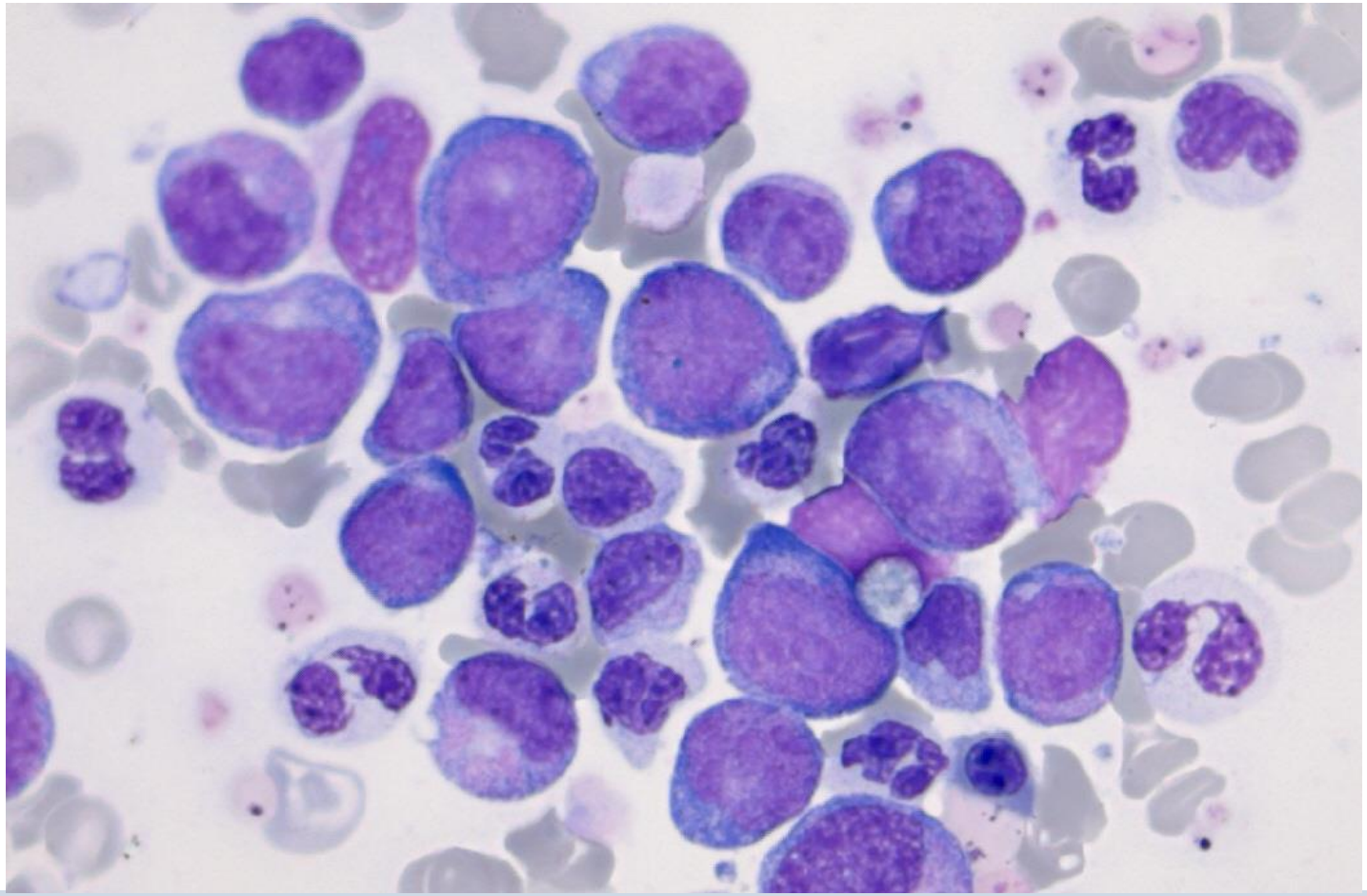


-hypogranulatie

-Pseudo Pelger

-bizarre vormen (hypersegm)

dysplasie granulopoiese



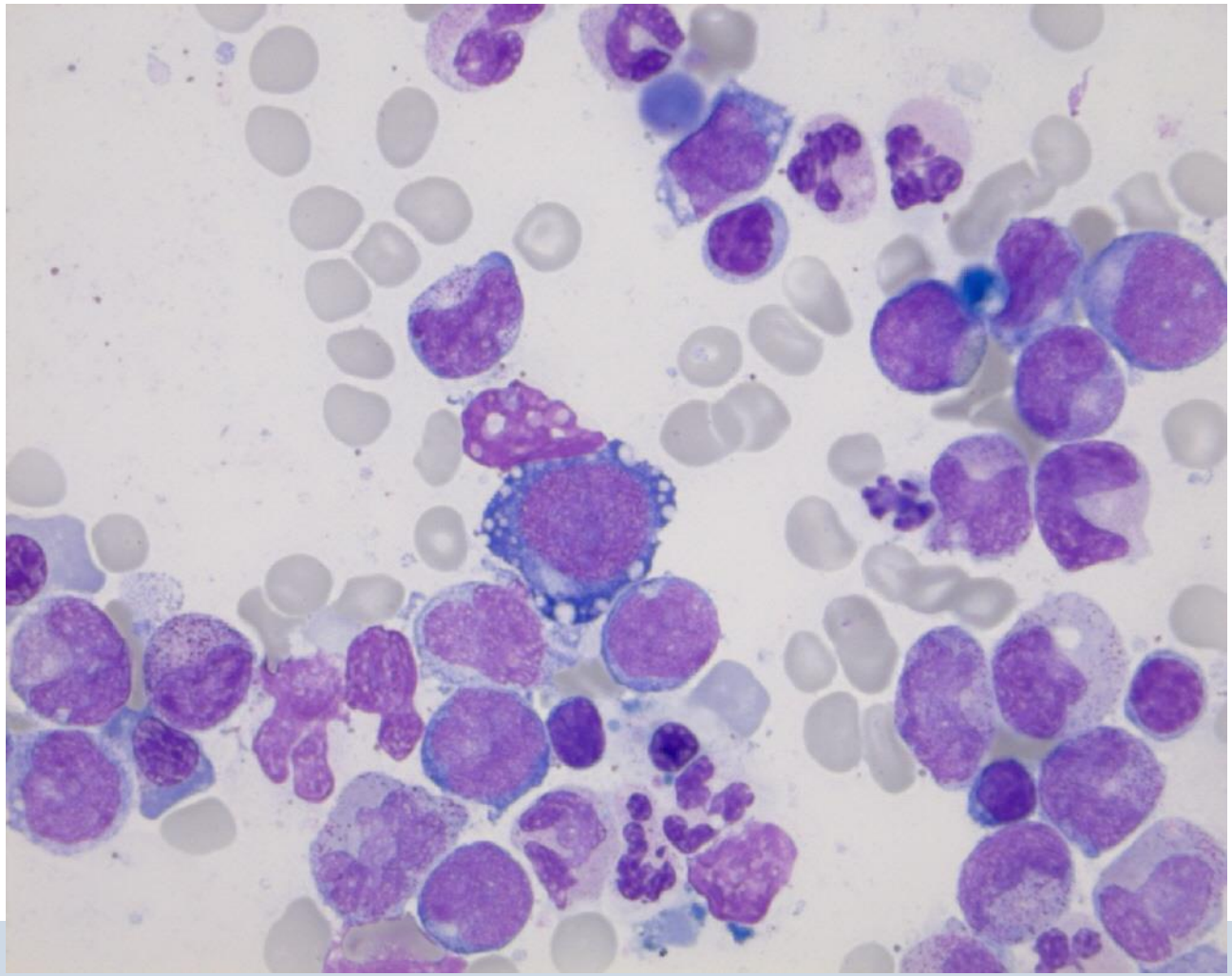
-hypogranulatie

-Pseudo Pelger

-bizarre vormen (hypersegm)

beenmerg

dysplasie granulopoiese



-hypogranulatie

-Pseudo Pelger-Huet

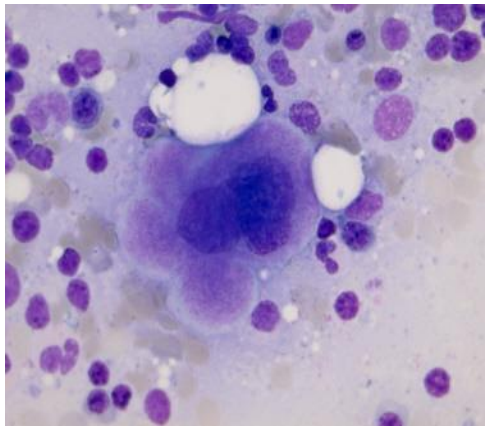
-bizarre vormen (hypersegm)

beenmerg

Dysplasie megakaryopoiese

- Erythropoiese
  - megaloblastoid, karyorhexis, nucleaire fragmenten, multinucleatie
  - Ring-sideroblasten
  - Cytoplasmatische vacuoles, PAS positiviteit
- Granulopoiese
  - hypogranulatie
  - hyposegmentatie (pseudo Pelger-Huet anomalie)
  - bizarre gesegmenteerde kernen
- Megakaryopoiese
  - micromegakaryocyten
  - monogelobuleerde of meerdere losliggende kernen

dysplasie megakaryopoiese monolobulair



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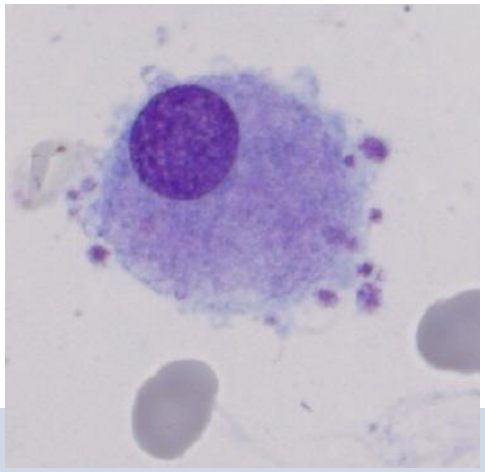
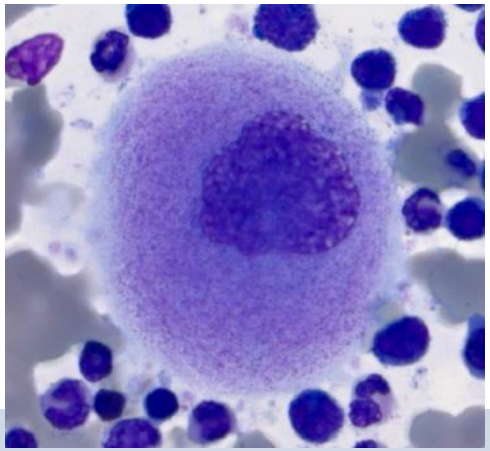
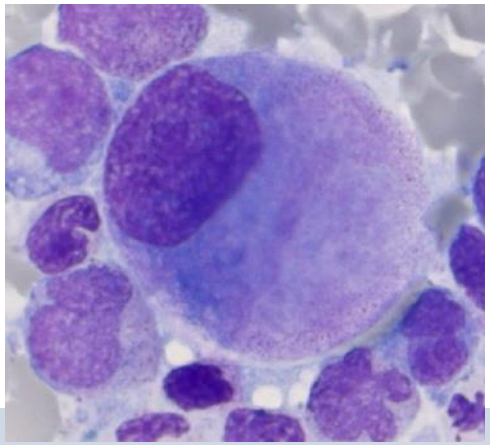
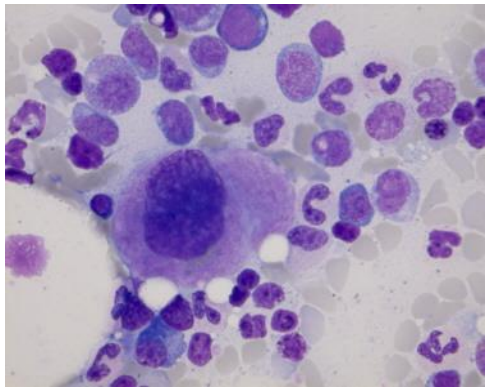






monolobulair

dysplasie megakaryopoiese micromegakaryocyten



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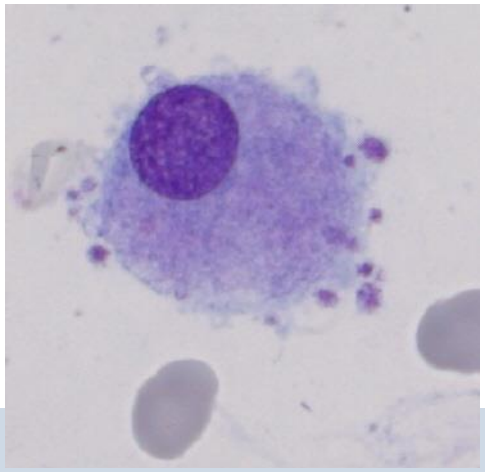
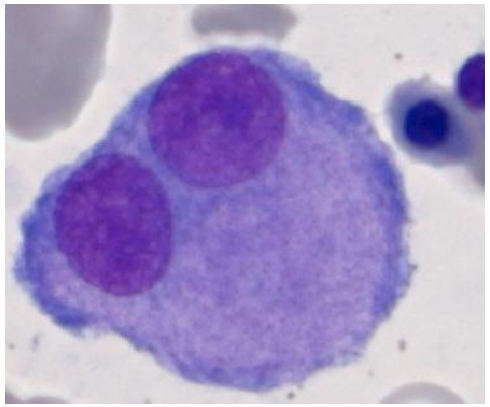
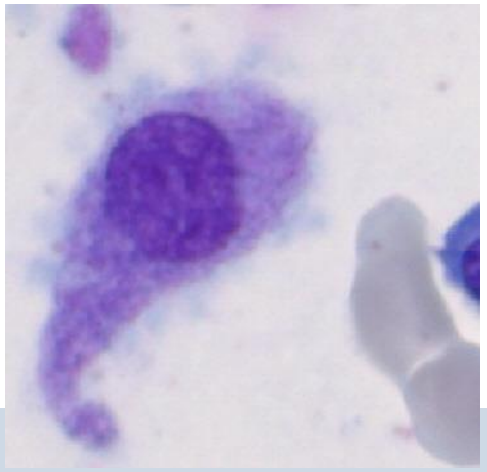
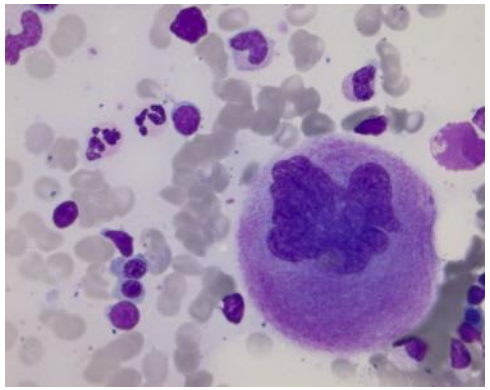






micromegakaryocyten

dysplasie megakaryopoiese
losse kernen



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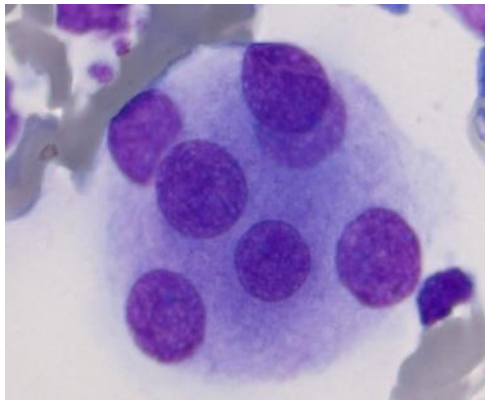
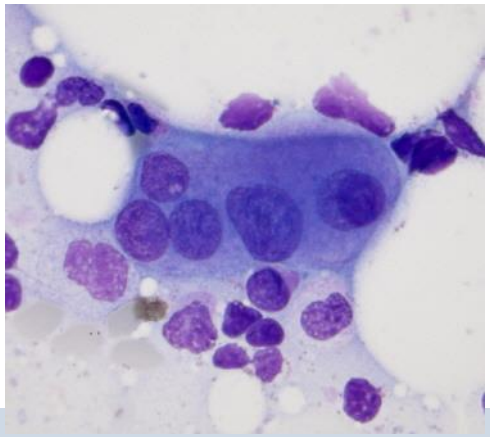
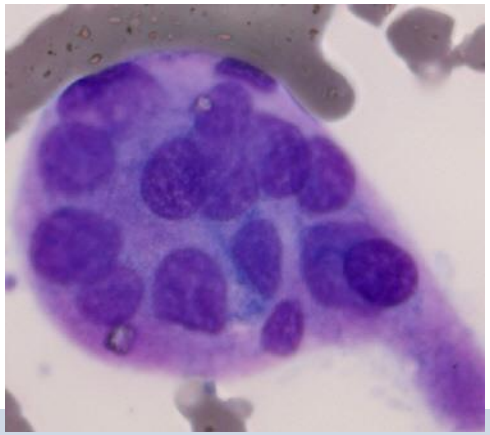
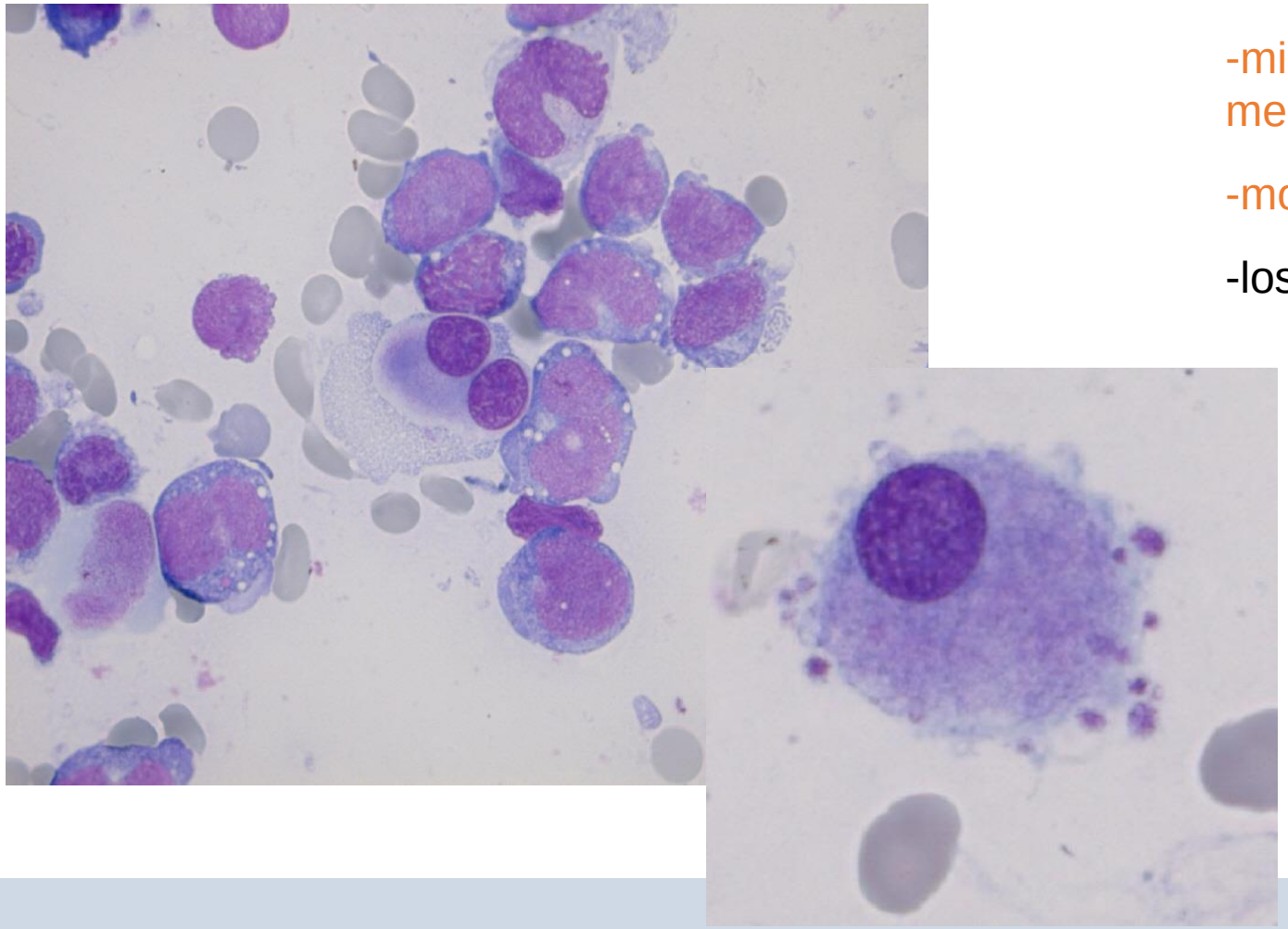






losse kernen

dysplasie megakaryopoiese



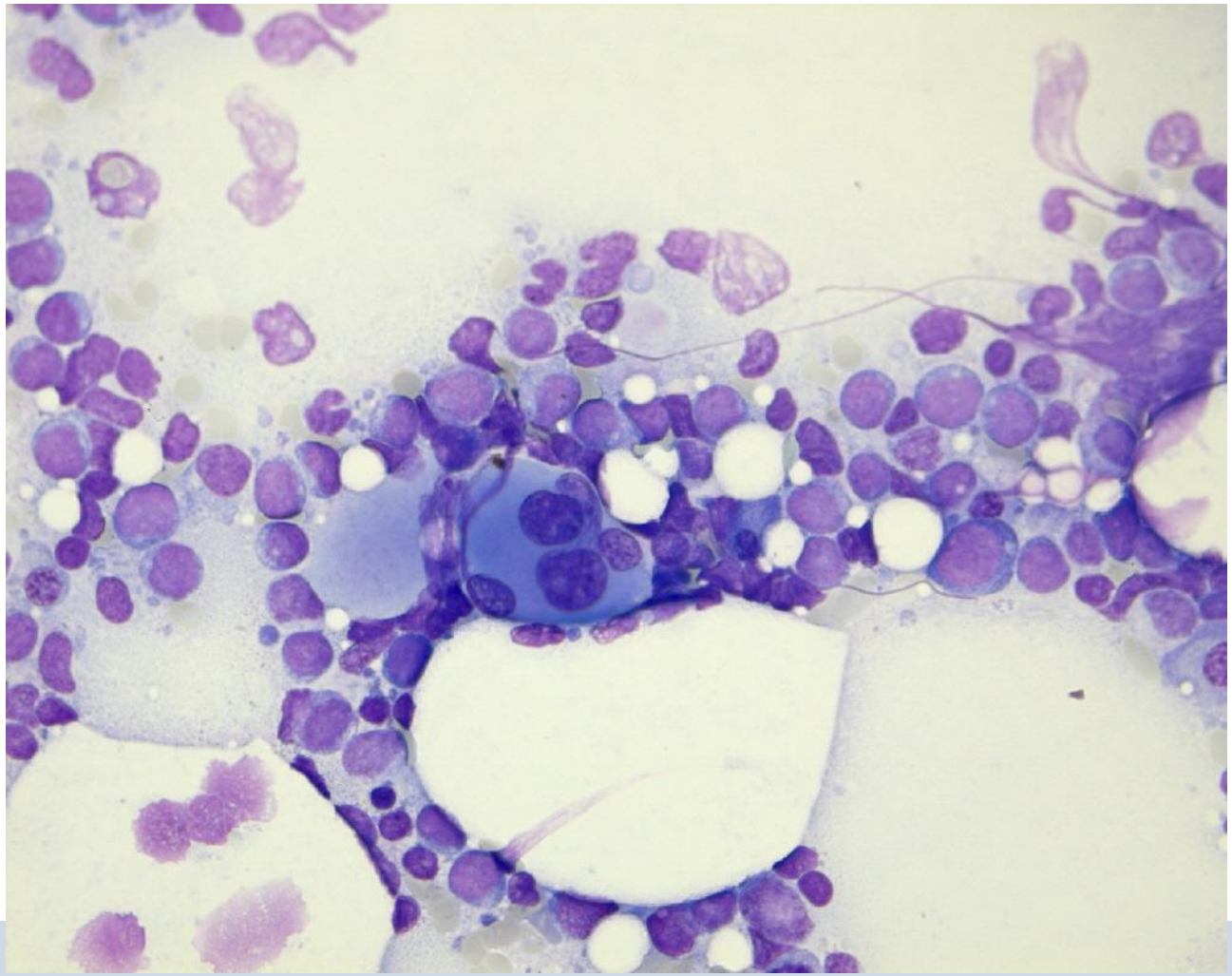
-micro-megakaryocyten

-monolobulair

-losse kernen

beenmerg

dysplasie megakaryopoiese

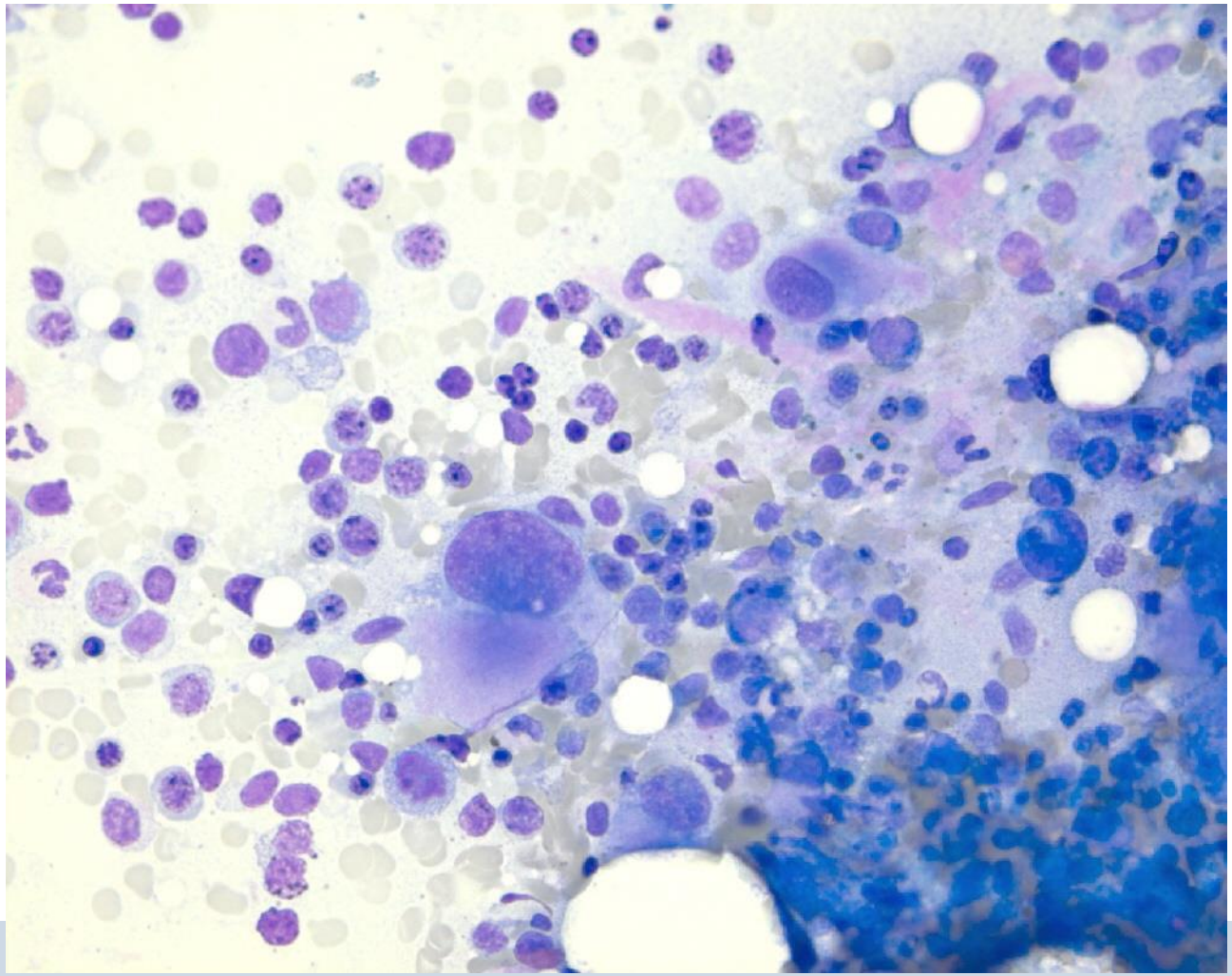


-micro-megakaryocyten

-monolobulair

-losse kernen

dysplasie megakaryopoiese

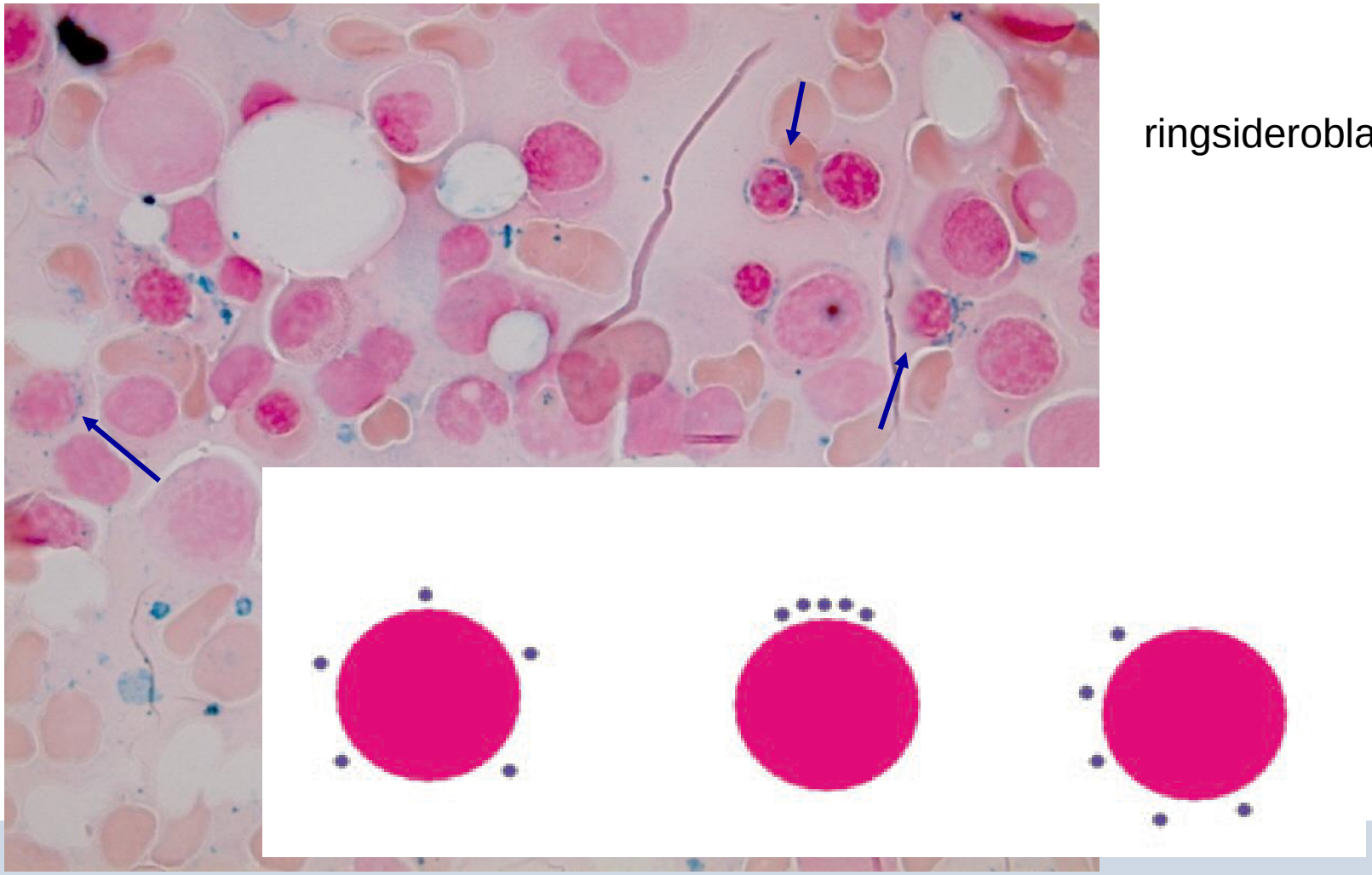


-micro-megakaryocyten

-monolobulair

-losse kernen

iron staining in RARS



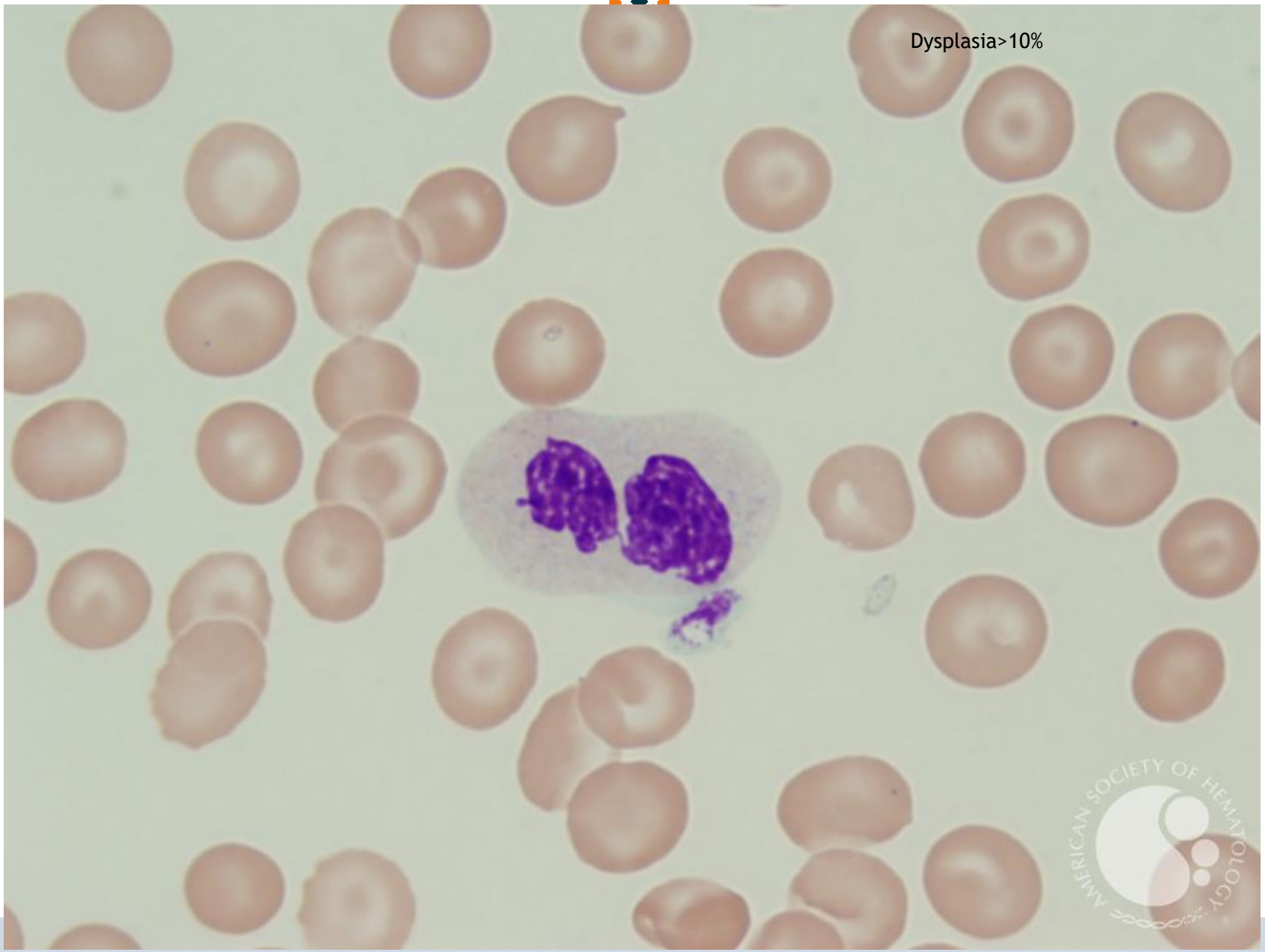
ringsideroblast

Casus 1

65 jarige pt,

Moe: Hb 5,4 mmol/l , MCV 102 fl, leuco

5.5 x 10^9/L (neutrofielen 2.4), trombo 55 x 10^9/L.


Dysplasia>10%
AMERICAN SOCIETY OF HEMATOLOGY

Cytogenetica: 46 XY

Cytopenie: 2 lijnen

Dysplasie: 1 lijn

Diagnose:……..

Cytogenetica: 46 XY

Cytopenie: 2 lijnen

Dysplasie: 1 lijn

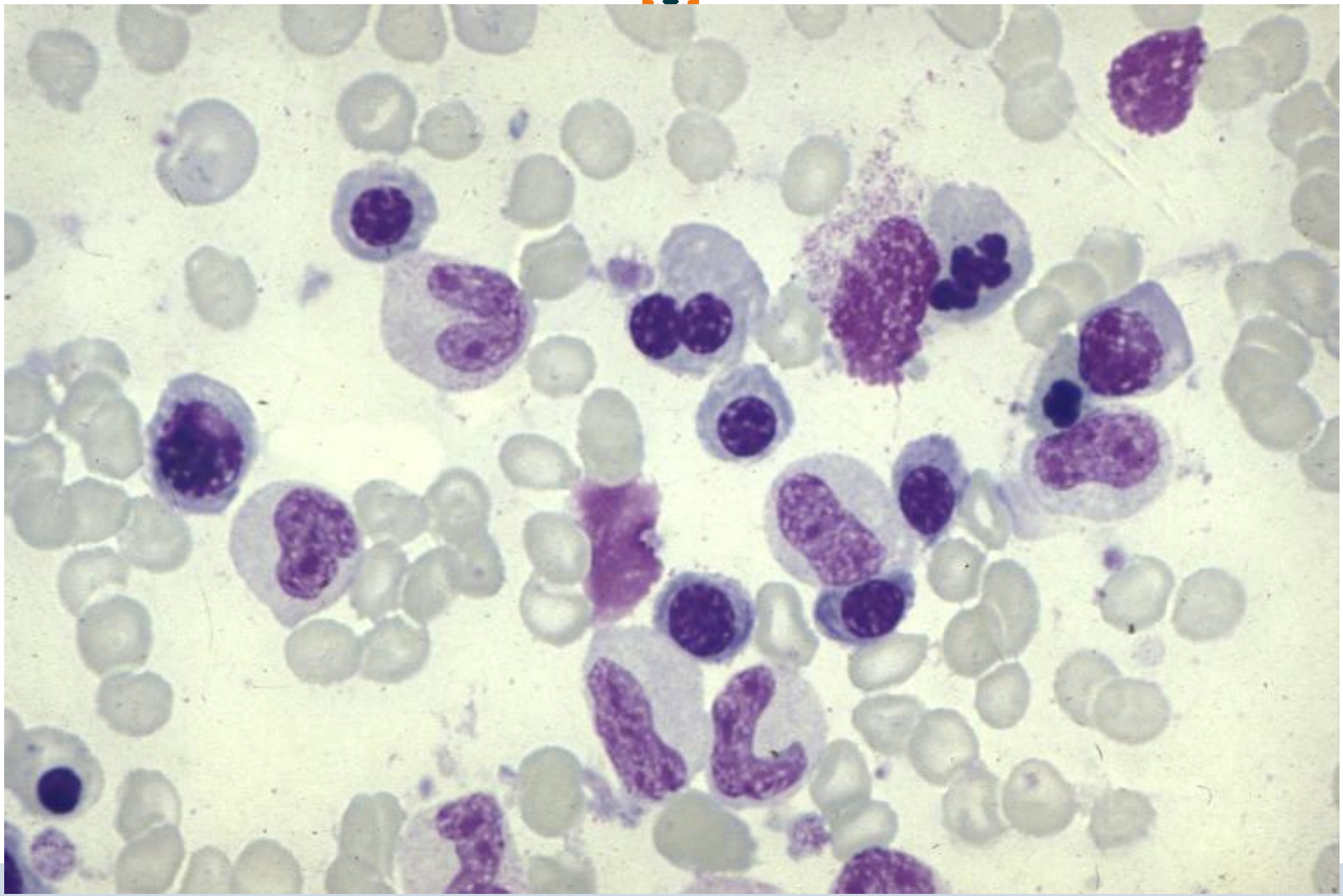
Diagnose: MDS-LB

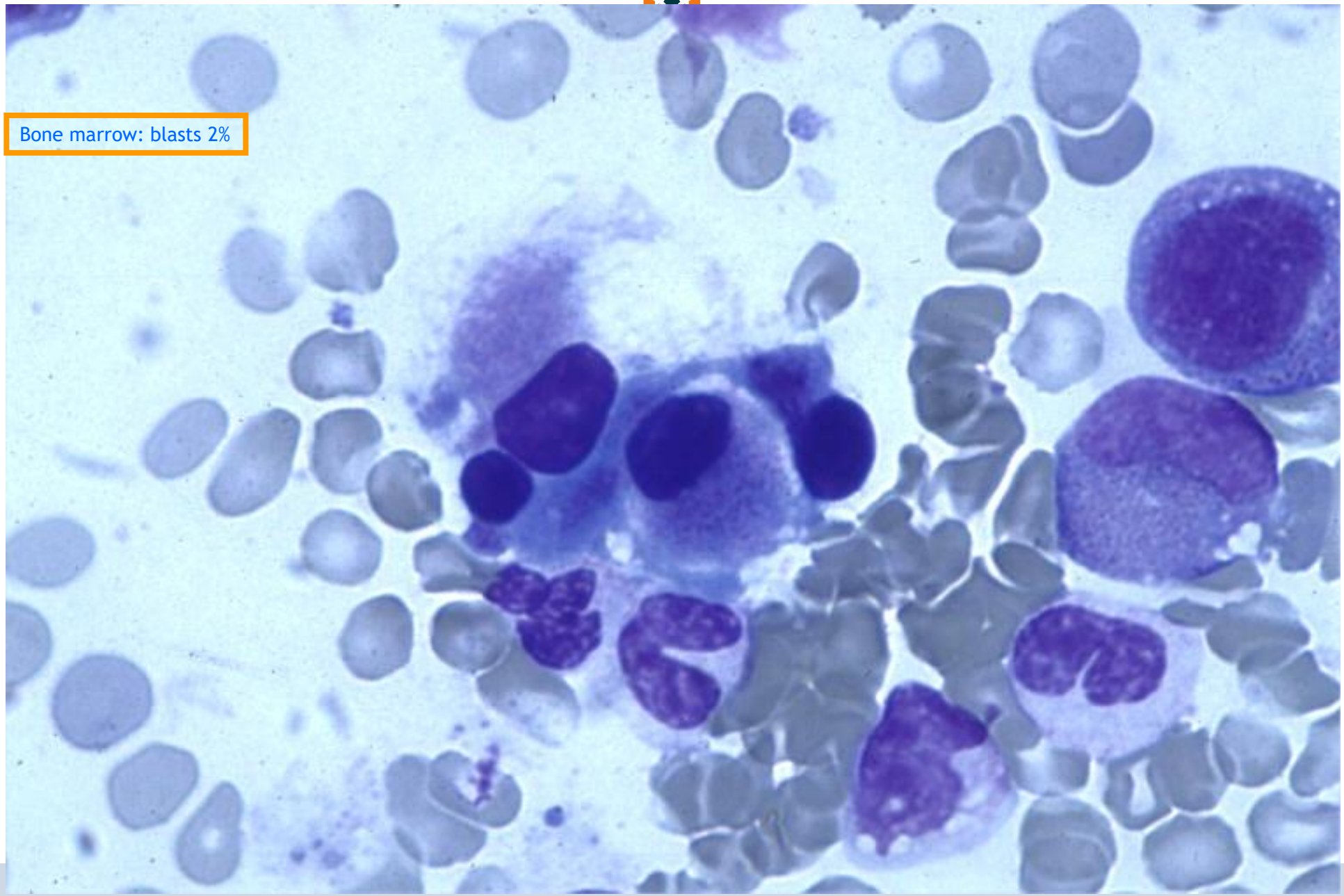
Casus 2

72-jarige patient,

Moe en snel blauwe plekken

Hb 6,2 mmol/l, MCV 102 fL, leuco 5.5 x 10^9/L, normale differentatie, trombo 55 x 10^9/L.




Bone marrow: blasts 2%

Cytopenie: 2

Dysplasie: 3

Diagnosis:……

Cytopenia: 2

Dysplasia: 3

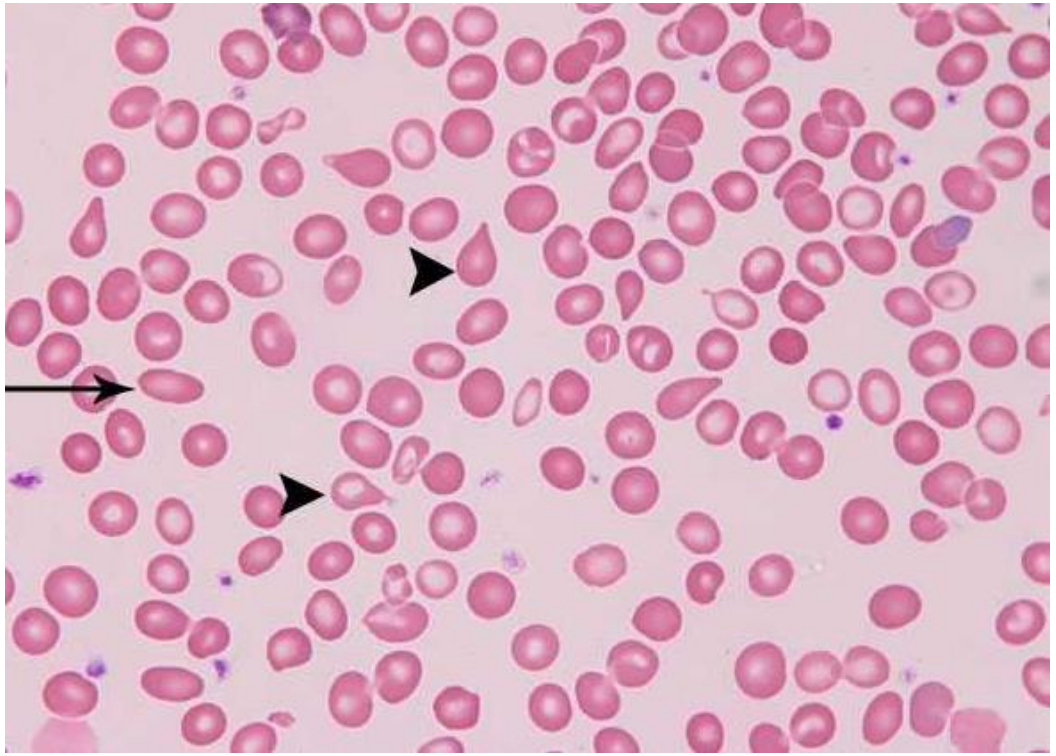
Diagnosis: MDS-LB

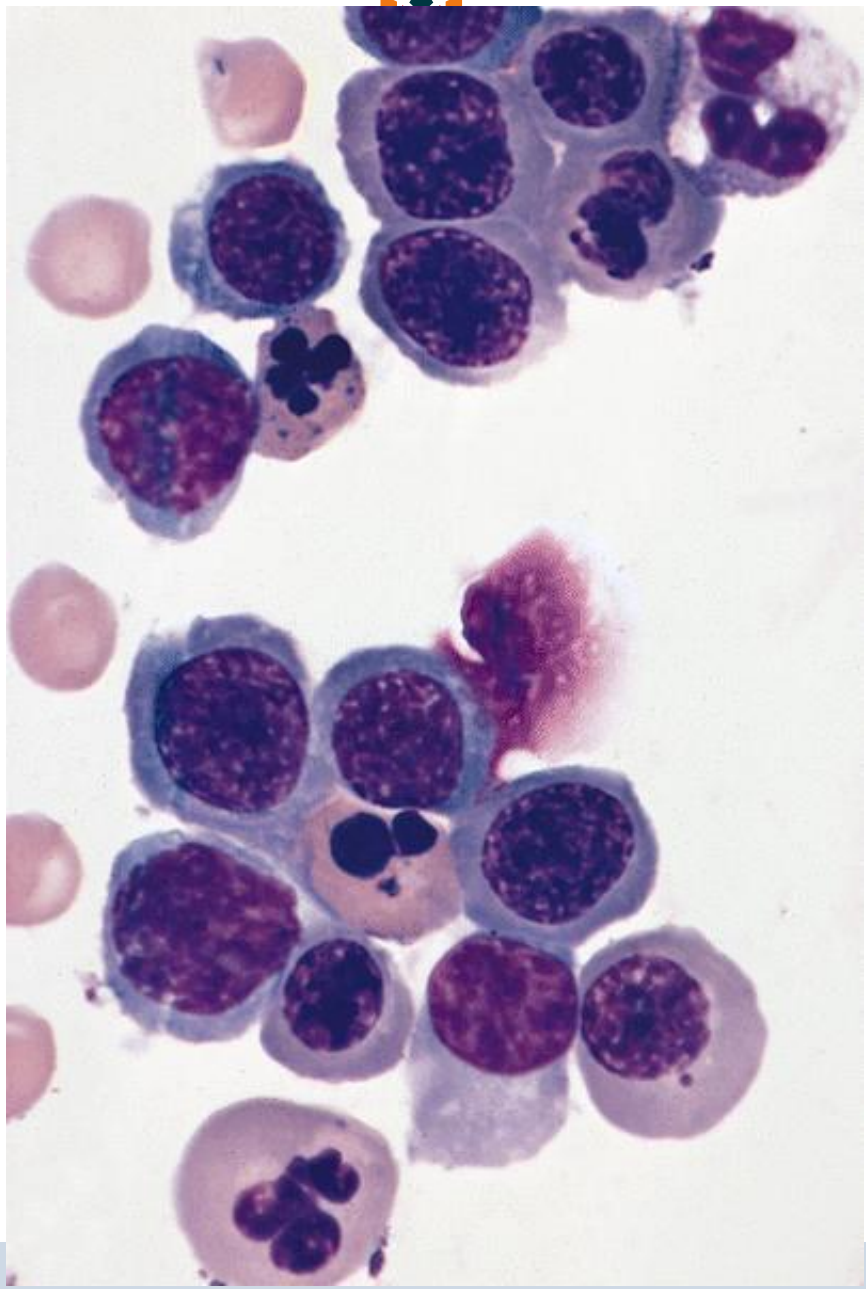
Casus 3

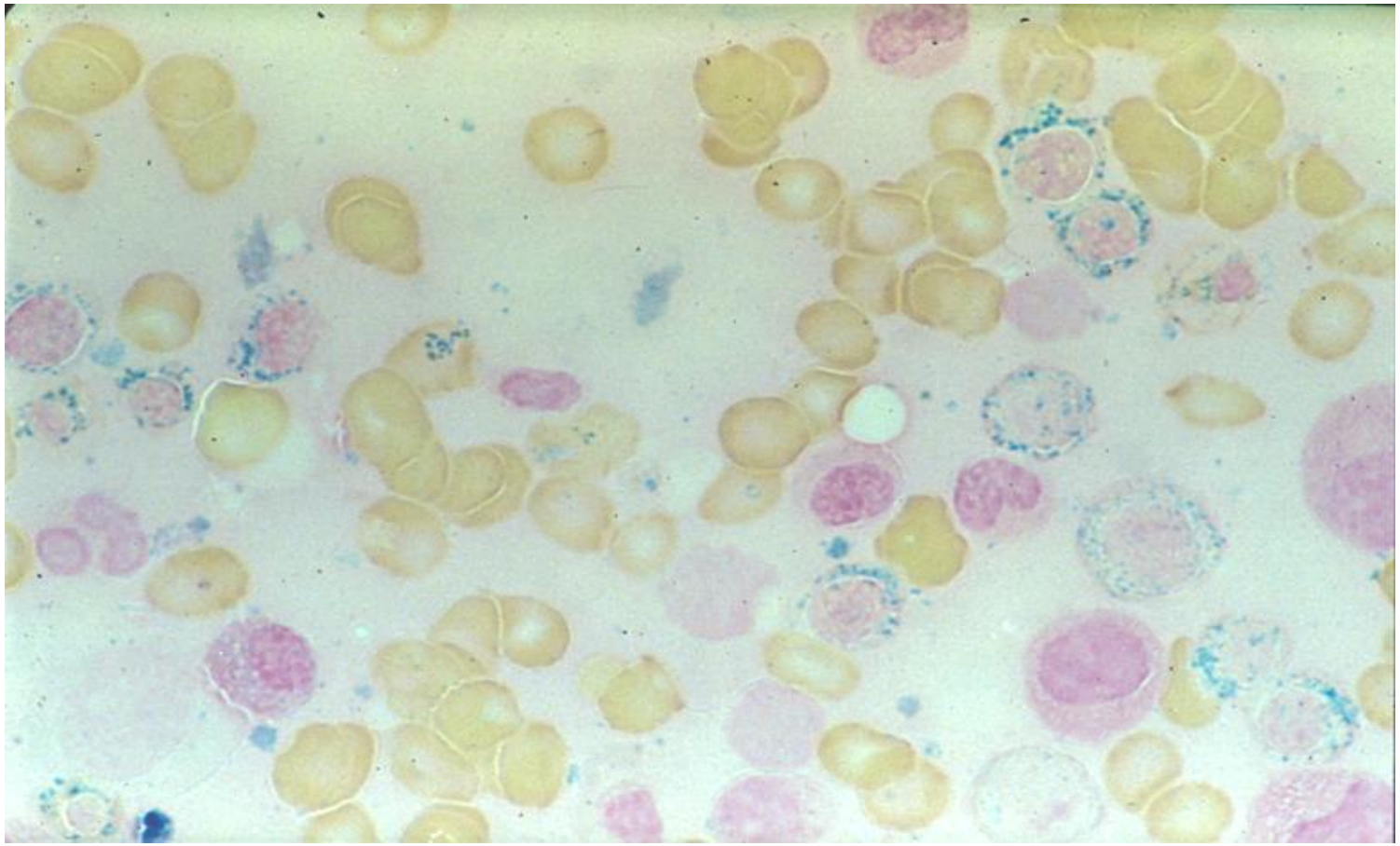
69 jarige vrouw

moe.

Hb 5,4 mmol/l, MCV 105 fL, leuco 3.5 x 10^9/L, normale differentiatie, trombo 355 x 10^9/L.







Cytopenie: twee lijnen

Dysplasie: een lijn, 50% ringsideroblasten

Diagnose: ……

(*SF3B1* mutation aanwezig)

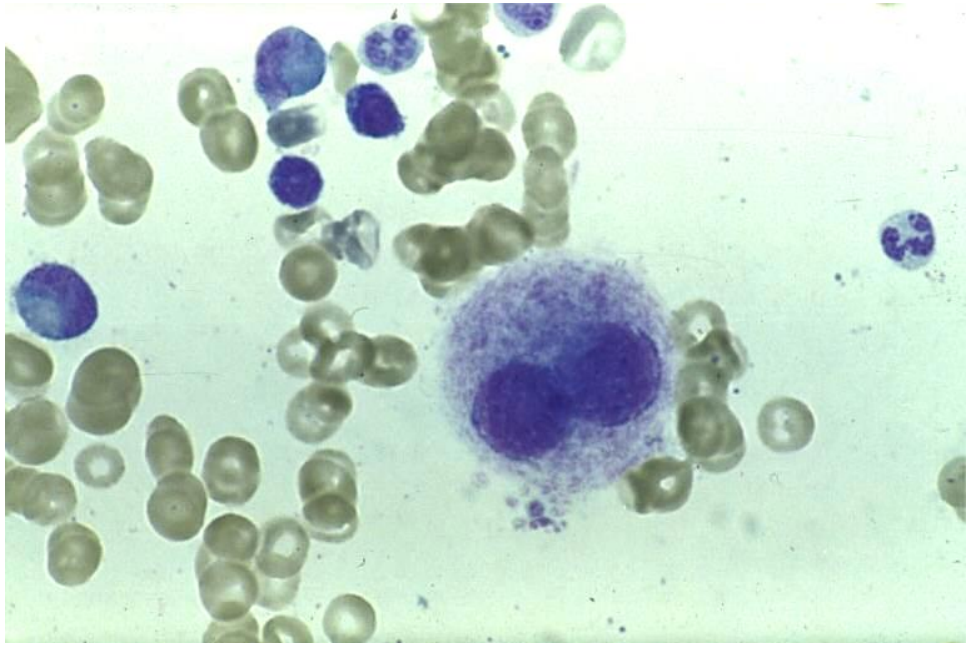
Cytopenie: twee lijnen

Dysplasie: een lijn, 50% ringsideroblasten

Diagnose: MDS met lage blasten en SF3B1 mutatie

(*SF3B1* mutation aanwezig)

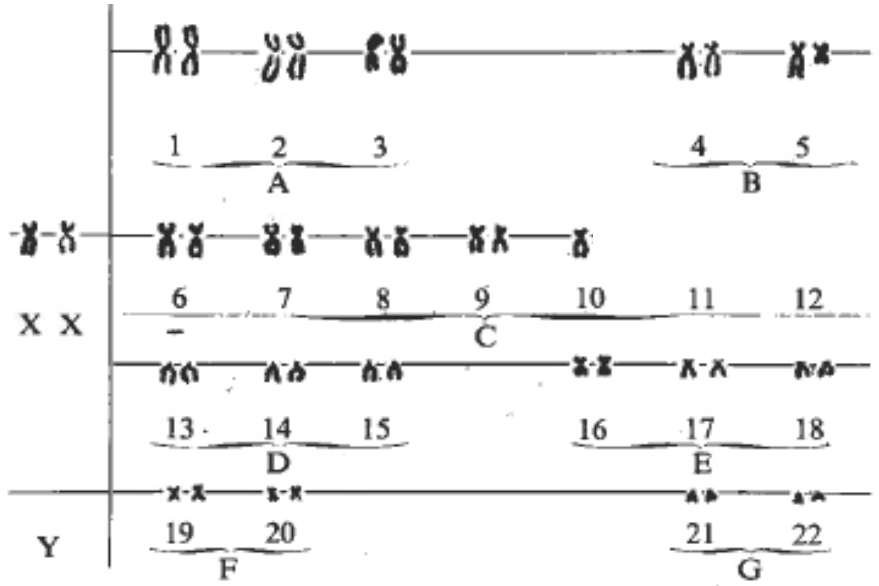
68 jarige vrouw, alleen moe
Hb 6,2 mmol/l, MCV 110 fL, leuco 6.0 x 10^9/L met 63 % neutro, 9 % mono, 28 % lymfo, trombo 515 x 10^9/L.



5q- syndrome

Distinct haematological disorder with deletion of long arm of No. 5 chromosome

Nature Vol. 251 October 4 1974



HERMAN VAN DEN BERGHE*
JEAN-JACQUES CASSIMAN
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Division of Human Genetics, Department of Human Biology,

JEAN-LOUIS MICHAUX
GERARD SOKAL

Department of Haematology, University of Louvain, B-3000 Belgium

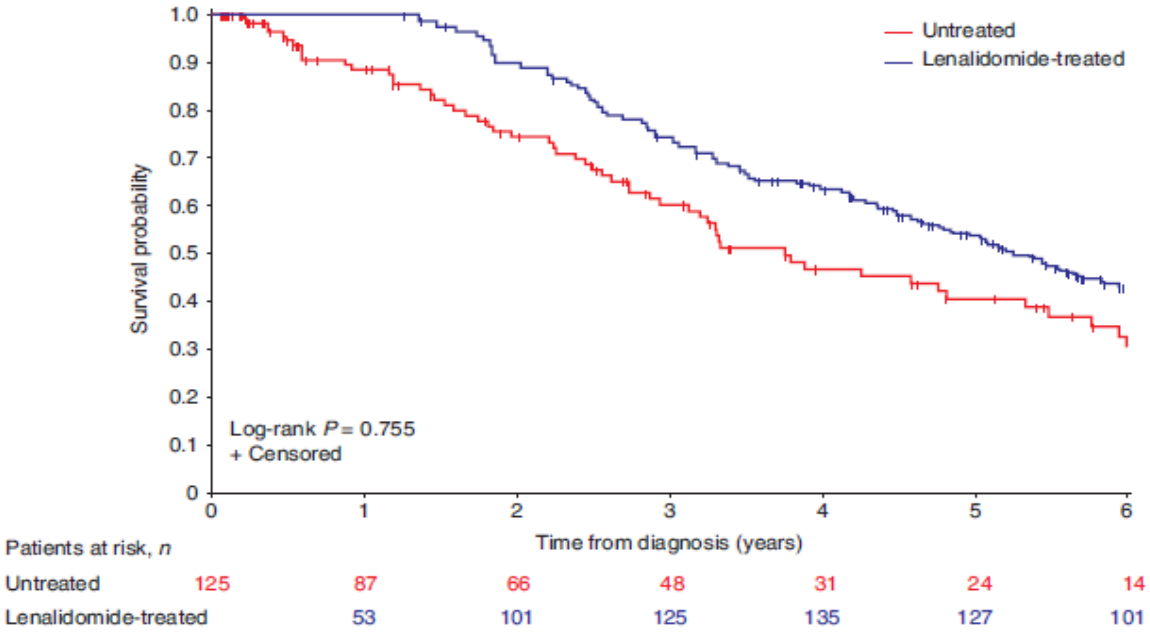
ORIGINAL ARTICLE

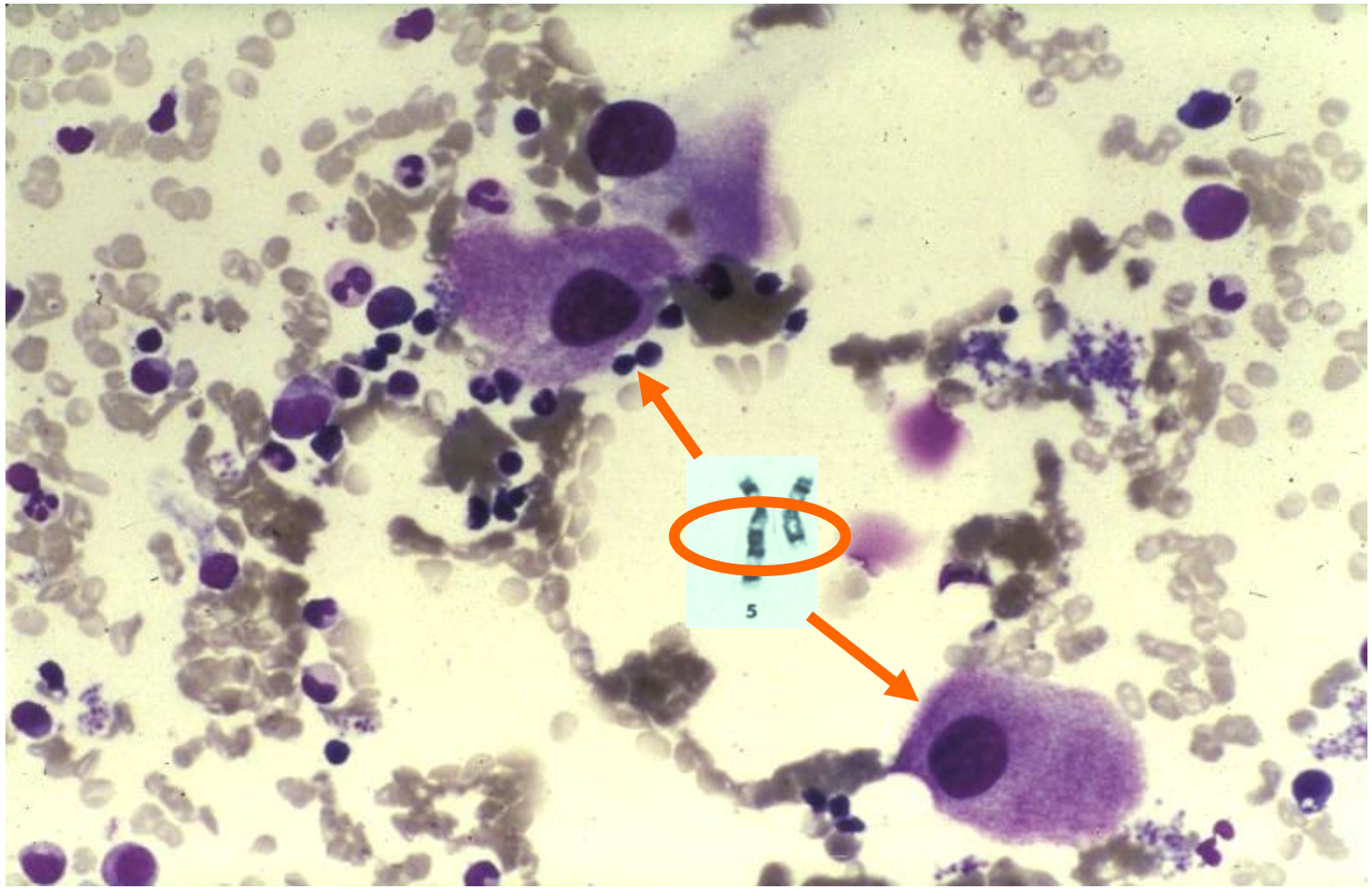
Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

Alan List, M.D., Gordon Dewald, Ph.D., John Bennett, M.D., Aristotle Giagounidis, M.D., Azra Raza, M.D., Eric Feldman, M.D., Bayard Powell, M.D., Peter Greenberg, M.D., Deborah Thomas, M.D., Richard Stone, M.D., Craig Reeder, M.D., Kenton Wride, M.S., John Patin, M.S., Michele Schmidt, R.N., Jerome Zeldis, M.D., and Robert Knight, M.D., for the Myelodysplastic Syndrome-003 Study Investigators*

N ENGL J MED 355;14 WWW.NEJM.ORG OCTOBER 5, 2006

MDS-003/004 Retrospective Analysis
Overall Survival




5

WHO 2022:

MDS met lage blasten en del5q

Cytogenetisch dan del 5q met max 1 andere afwijking maar niet monosomie7 of del7q

Prognostic evaluation of patients with MDS: IPSS-Revised

Revised International Prognostic Scoring System for Myelodysplastic Syndromes

Peter L. Greenberg,[1] Heinz Tuechler,[2] Julie Schanz,[3] Guillermo Sanz,[4] Guillermo Garcia-Manero,[5] Francesc Solé,[6] John M. Bennett,[7] David Bowen,[8] Pierre Fenaux,[9] Francois Dreyfus,[10] Hagop Kantarjian,[5] Andrea Kuendgen,[11] Alessandro Levis,[12] Luca Malcovati,[13] Mario Cazzola,[13] Jaroslav Cermak,[14] Christa Fonatsch,[15] Michelle M. Le Beau,[16] Marilyn L. Slovak,[17] Otto Krieger,[18] Michael Luebbert,[19] Jaroslaw Maciejewski,[20] Silvia M. M. Magalhaes,[21] Yasushi Miyazaki,[22] Michael Pfeilstöcker,[2] Mikkael Sekeres,[20] Wolfgang R. Sperr,[15] Reinhard Stauder,[23] Sudhir Tauro,[24] Peter Valent,[15] Teresa Vallespi,[25] Arjan A. van de Loosdrecht,[26] Ulrich Germing,[11] and Detlef Haase[3]

Scoring system

Cytogenetics	V good	Good	Int	Poor	V poor
	0	1	2	3	4
BM blasts (%)	≤2%	>2-<5%	5-10%	>10%	
	0	1	2	3	
Hb level (g/dL)	≥10	8-<10	<8		
	0	1	1.5		
ANC (x10^9/L)	≥0.8	<0.8			
	0	0.5			
Platelets (x10^9/L)	≥100	50-<100	<50		
	0	0.5	1		

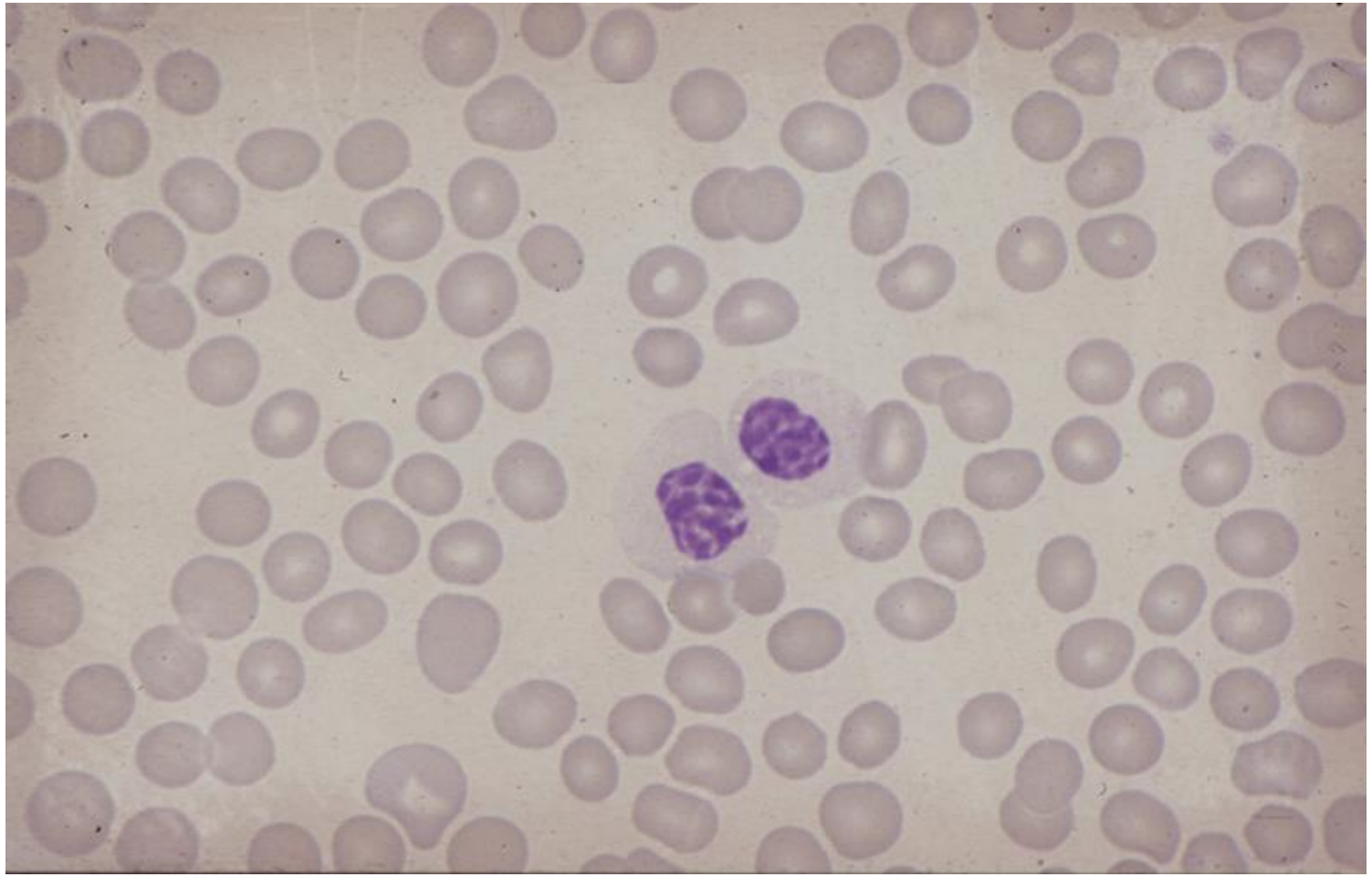
Overall risk score

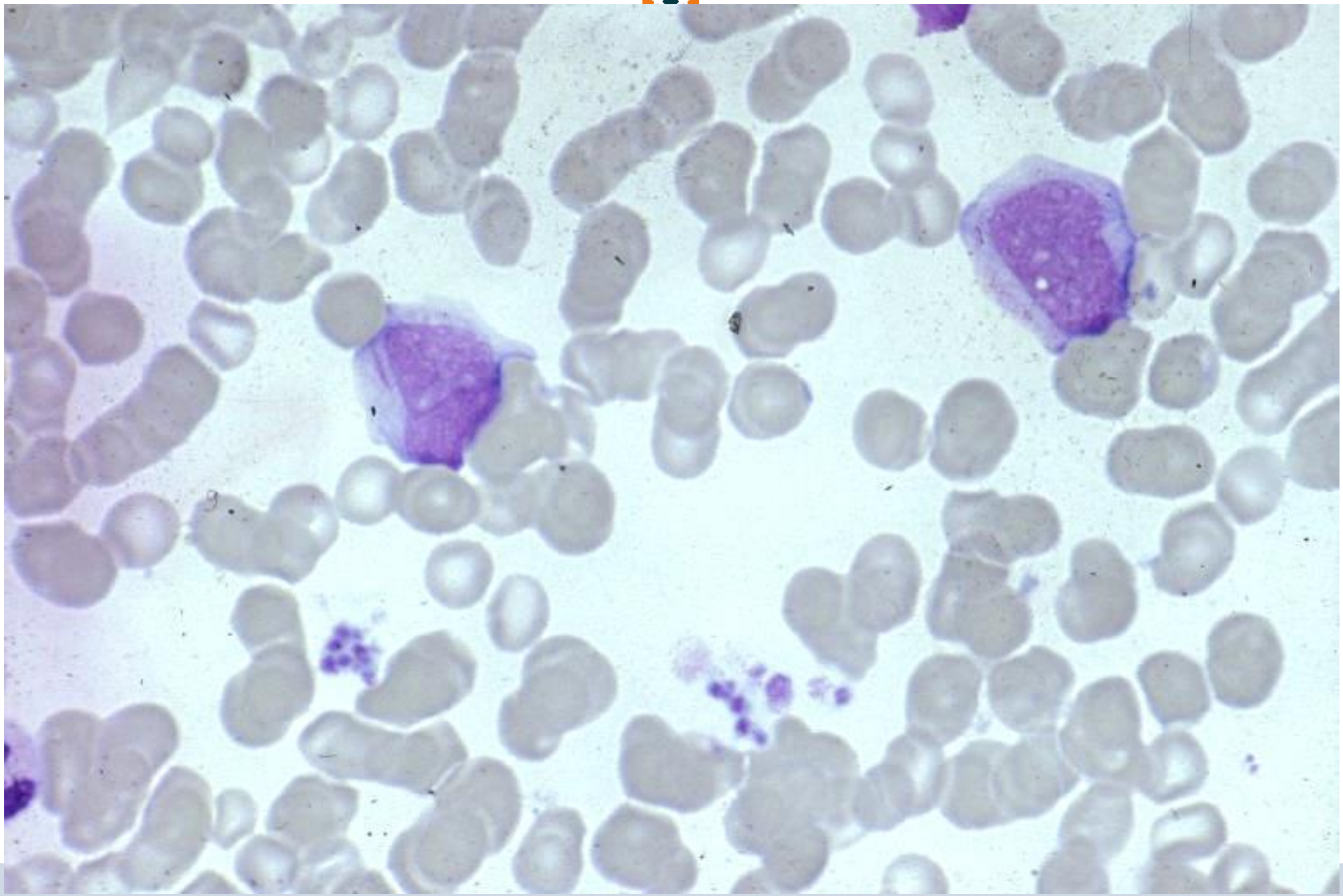
Very low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very high	>6

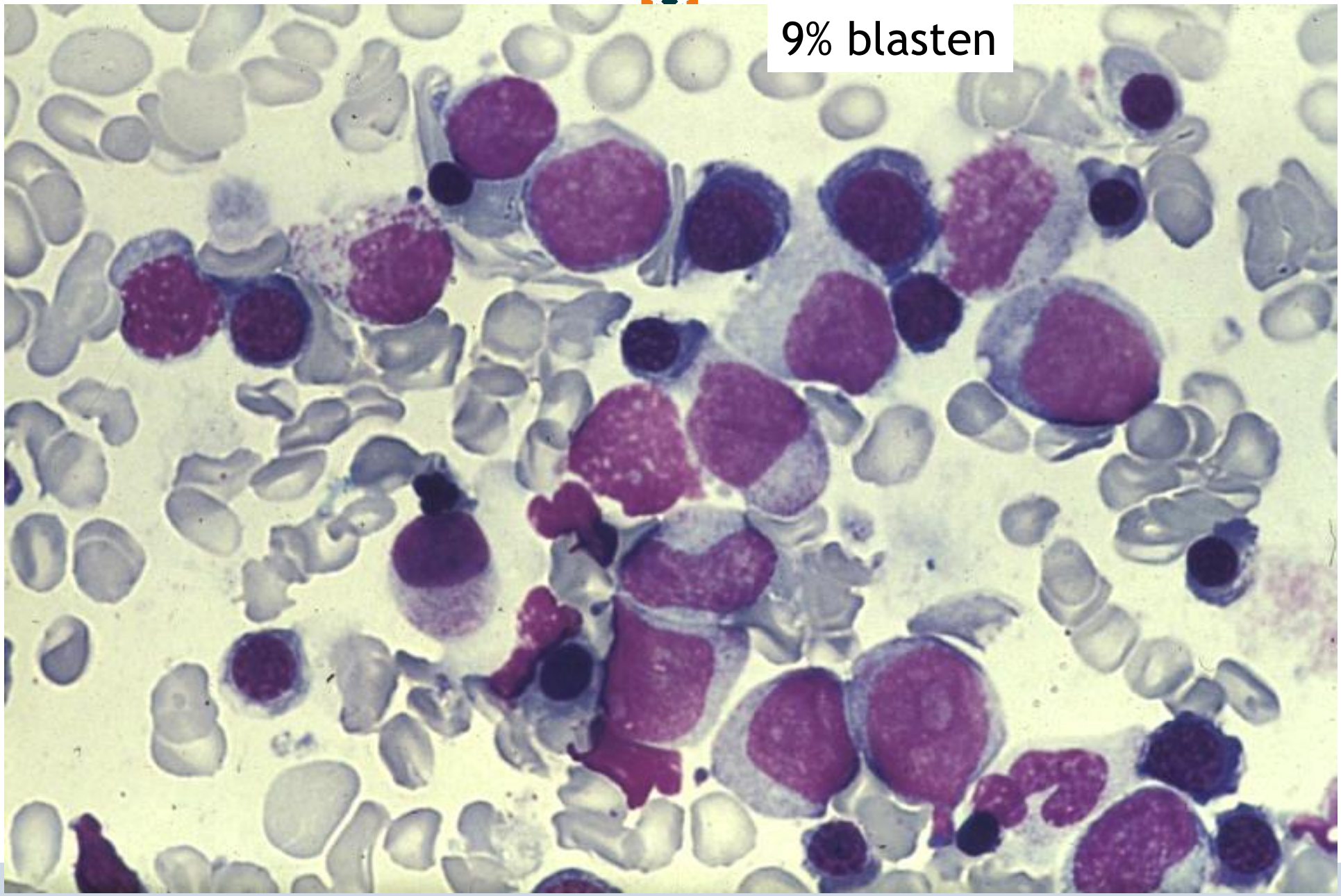
Greenberg P, et al. Blood 2012;120:2454–65

Casus 4

63 jarige vrouw
Meerdere infecties in laatste jaar
Hb 4,8 mmol/l, MCV 103 fL, leuco 2.0 x 10^9/L met 2% blasten, 21% neutro, 26 % mono, 51% lymfo, thrombo 89 x 10^9/L.

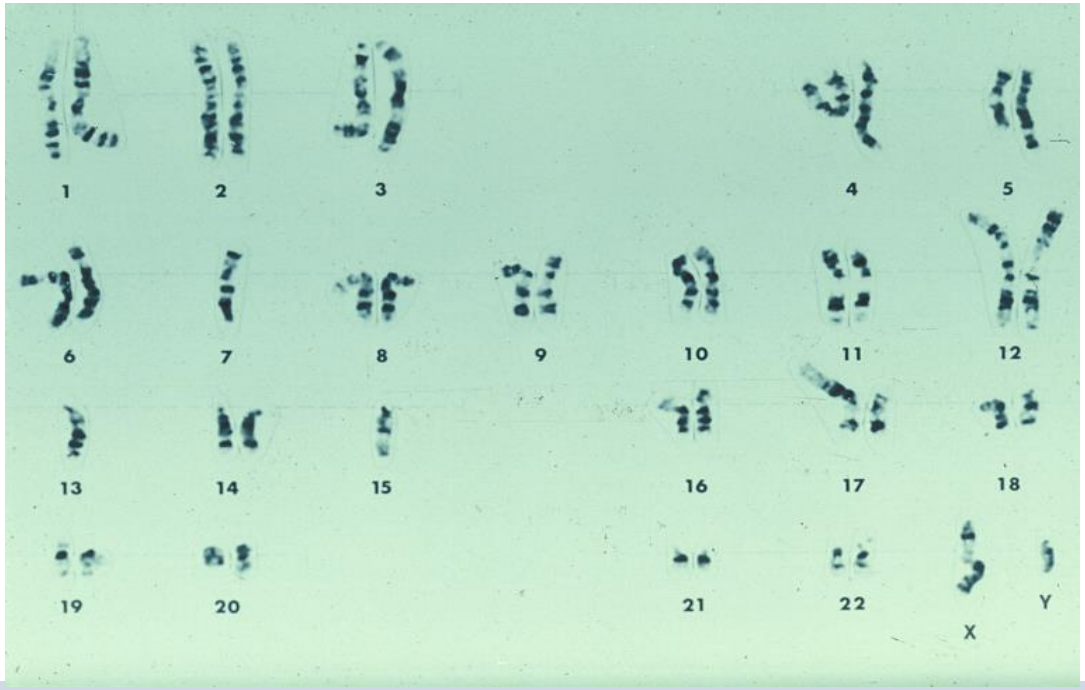




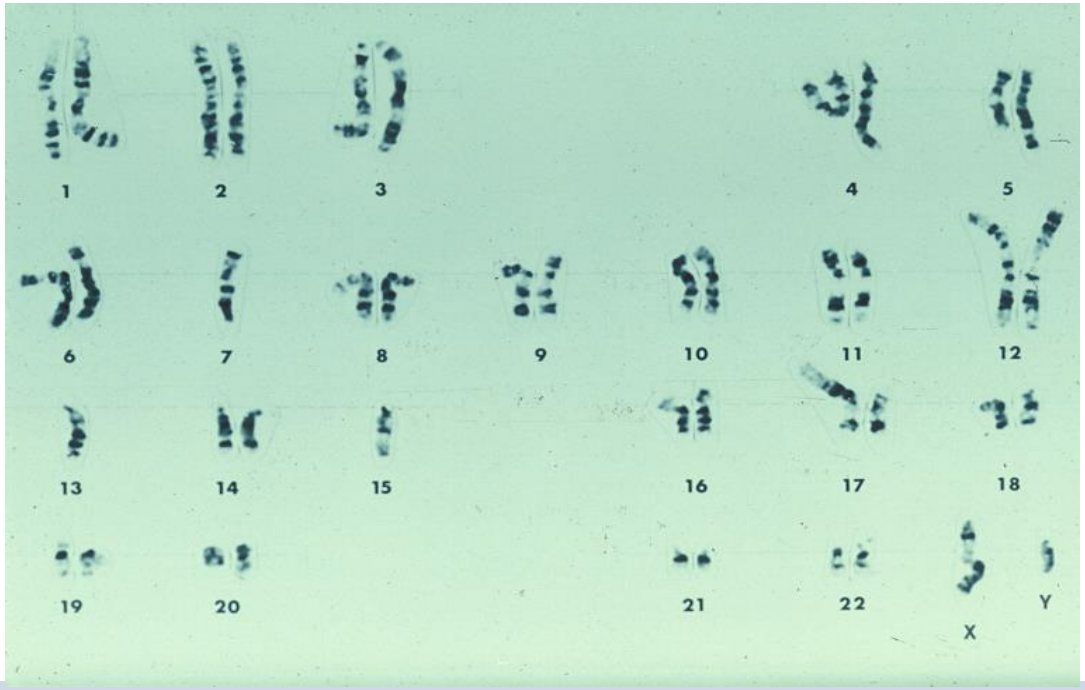

9% blasten

Dus:

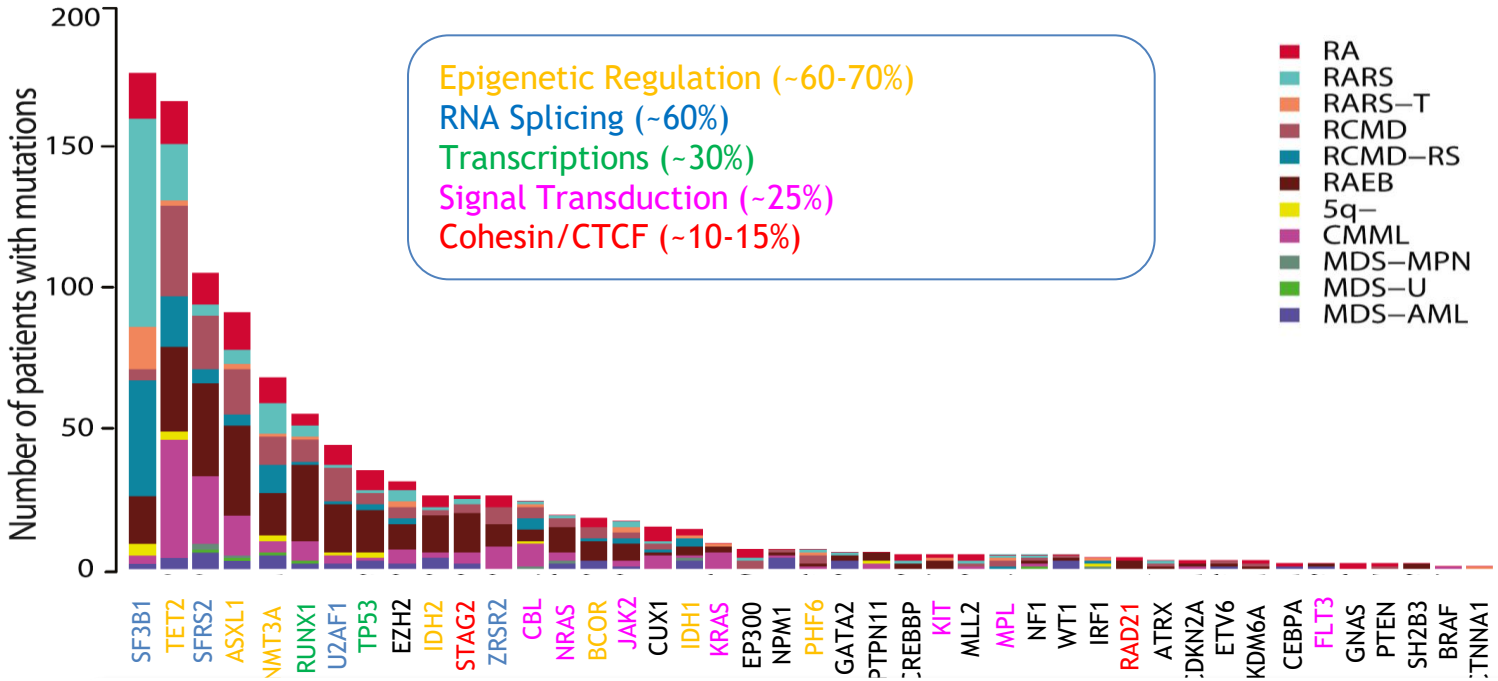
Pb: 2 % blasten
BM: 9 % blasten
Diagnosis:……..



Pb: 2 % blasten
BM: 9 % blasten
Diagnosis: MDS-IB2
(auerse staaf)



Genomic architecture of MDS - Genes recurrently mutated in MDS



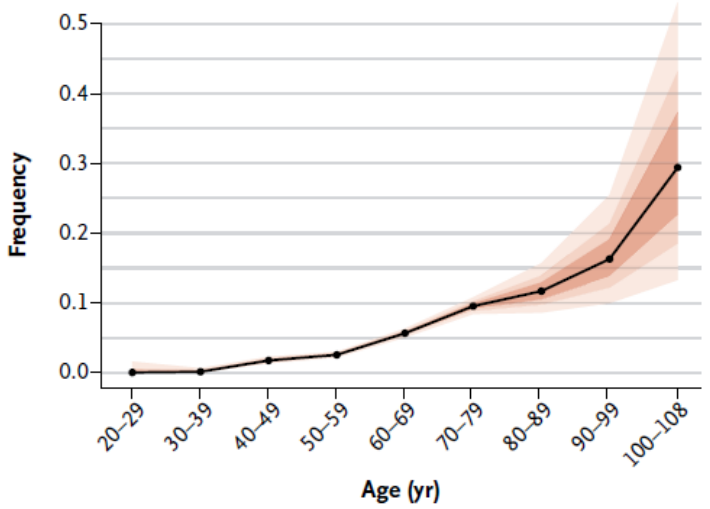
A variety of genetic alterations has been identified, although none has been specifically associated with MDS

Modified from Papaemmanuil, et al. Blood. 2013; 122: 3616-3627.

Heel handig: https://mds-risk-model.com/

ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes



No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

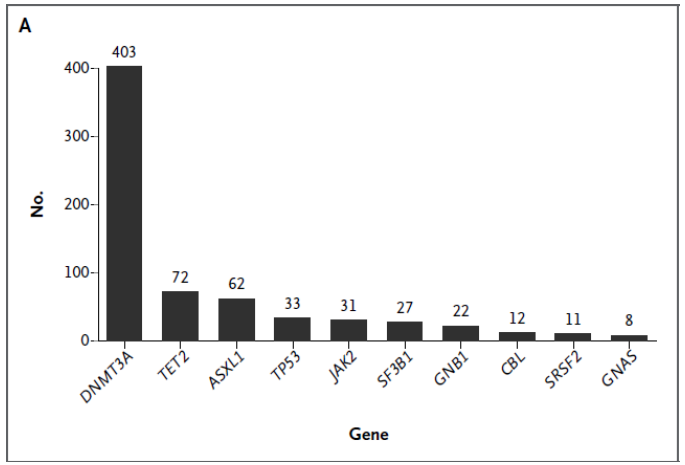


Figure 1. Prevalence of Somatic Mutations, According to Age.

Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

Jaiswal et al. New Engl J Med 2014;371:2488

Other members of MDS family

Myelodysplastic /myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemie (CMML)
- Atypical chronic myeloid leukemia (aCML, *BCR-ABL1*-negative)
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

Acute myeloid leukemia (AML) and related neoplasms

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

- MDS/AML following cytotoxic therapy with…..cytogenetic abnormality

Gevorderden cursus