Myelodysplastic syndrome or the tale of 3 classifications

Julia T Geyer, MD

Associate Professor

Division of Pathology and Laboratory Medicine

Weill Cornell Medicine

New York, USA

APOYO

INTRODUCTION

- MDS is a clonal hematopoietic neoplasm
  - Persistent unexplained cytopenia
  - Morphologic dysplasia
  - Risk of progression to acute myeloid leukemia
- Cytopenias need to be chronic (typically ≥4 months)
- Dysplasia is significant if ≥10% of the cells are dysplastic for ALL lineages
- Proof of clonality is not required for diagnosis of MDS (but is reassuring!)

MORE DEFINITIONS

Dysplasia with the best specificity for MDS

1) Hypogranular and hyposegmended neutrophils
2) Micromegakaryocytes

Cytopenia (valid for MDS, but also clonal cytopenia of undetermined significance-CCUS and MDS/MPN) is defined as

- Anemia = hemoglobin <12 g/dL in females / <13 g/dL in males
- Neutropenia = absolute neutrophil count <1.8 x 10^9/L
- Thrombocytopenia = platelets <150 x 10^9/L

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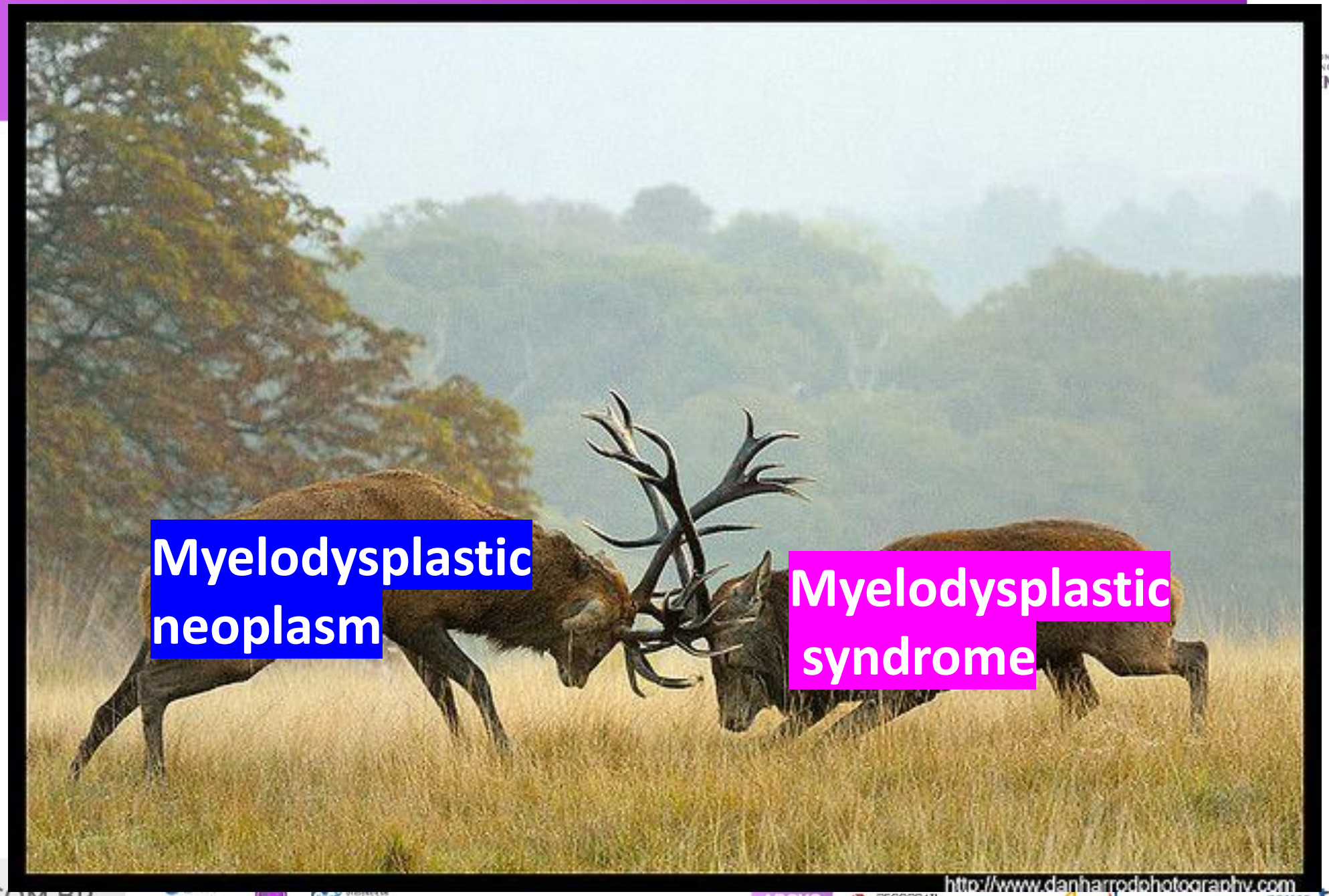
Myelodysplastic neoplasm
Myelodysplastic syndrome
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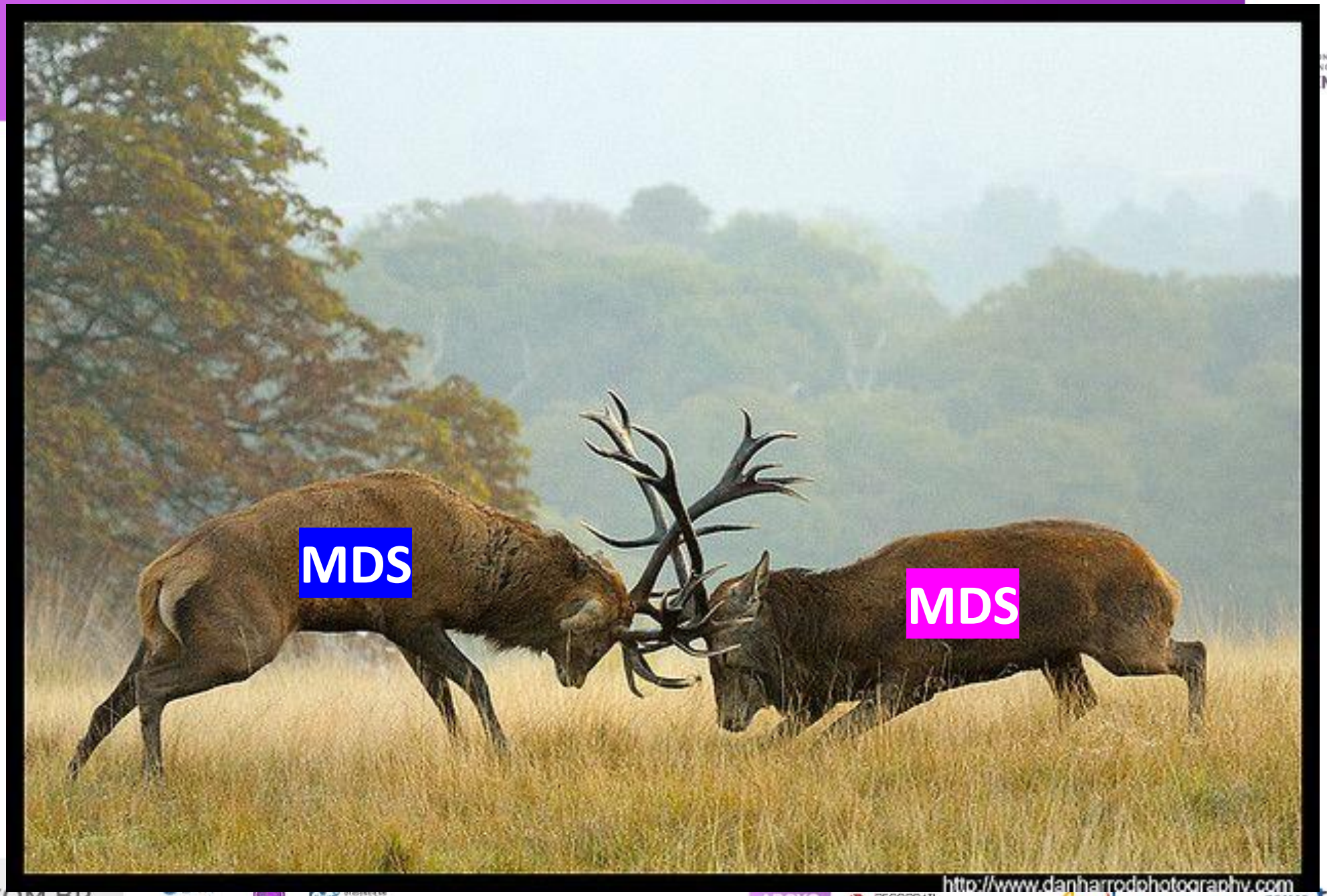
MDS
MDS
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Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

WHO 5th edition

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	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics[b]***	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1[c]	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), -7/del(7q), abn3q26.2, or complex	*SF3B1* (≥10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1[c]	≥1	Thrombocytosis allowed	<5% BM <2% PB[d]	del(5q), with up to 1 additional, except -7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS - without dysplasia	0	≥1	0	<5% BM <2% PB[d]	-7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥10% VAF)
MDS, NOS - with single lineage dysplasia	1	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53;*not meeting criteria for MDS-*SF3B1*
MDS, NOS - with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53,*; not meeting criteria for MDS-*SF3B1*

MDS with excess blasts (MDS-EB)	Typically ≥1[c]	≥1	0	5-9% BM, 2-9% PB[d]	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1[c]	≥1	0	10-19% BM or PB[e]	Any, except AML-defining[f]	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

[a]Cytoses: Sustained white blood count ≥13 x 10^9/L, monocytosis (≥0.5 x 10^9/L and ≥10% of leukocytes), or platelets ≥450 x 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.

[b]*BCR*::*ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.

[c]Although dysplasia is typically present in these entities, it is not required.

[d]Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confimed on two separate occasions also qualifies for MDS-EB.

[e]For pediatric patients (<18 years), the blast thresholds for MDS-EB are 5-19% in BM and 2-19% in PB, and the entity MDS/AML does not apply.

[f]AML-defining cytogenetics are listed in the AML section.

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Table 21. Myeloid neoplasms with mutated *TP53*

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation[a], or *TP53* mutation (VAF >10%) and complex karyotype often with loss of 17p[b]
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF >10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF >10%)

[a]Defined as two distinct *TP53* mutations (each VAF >10%) OR a single *TP53* mutation with either 1) 17p deletion on cytogenetics; 2) VAF of >50%; or 3) Copy-neutral loss of heterozygosity (LOH) at the 17p *TP53* locus.

[b]If *TP53* locus LOH information is not available

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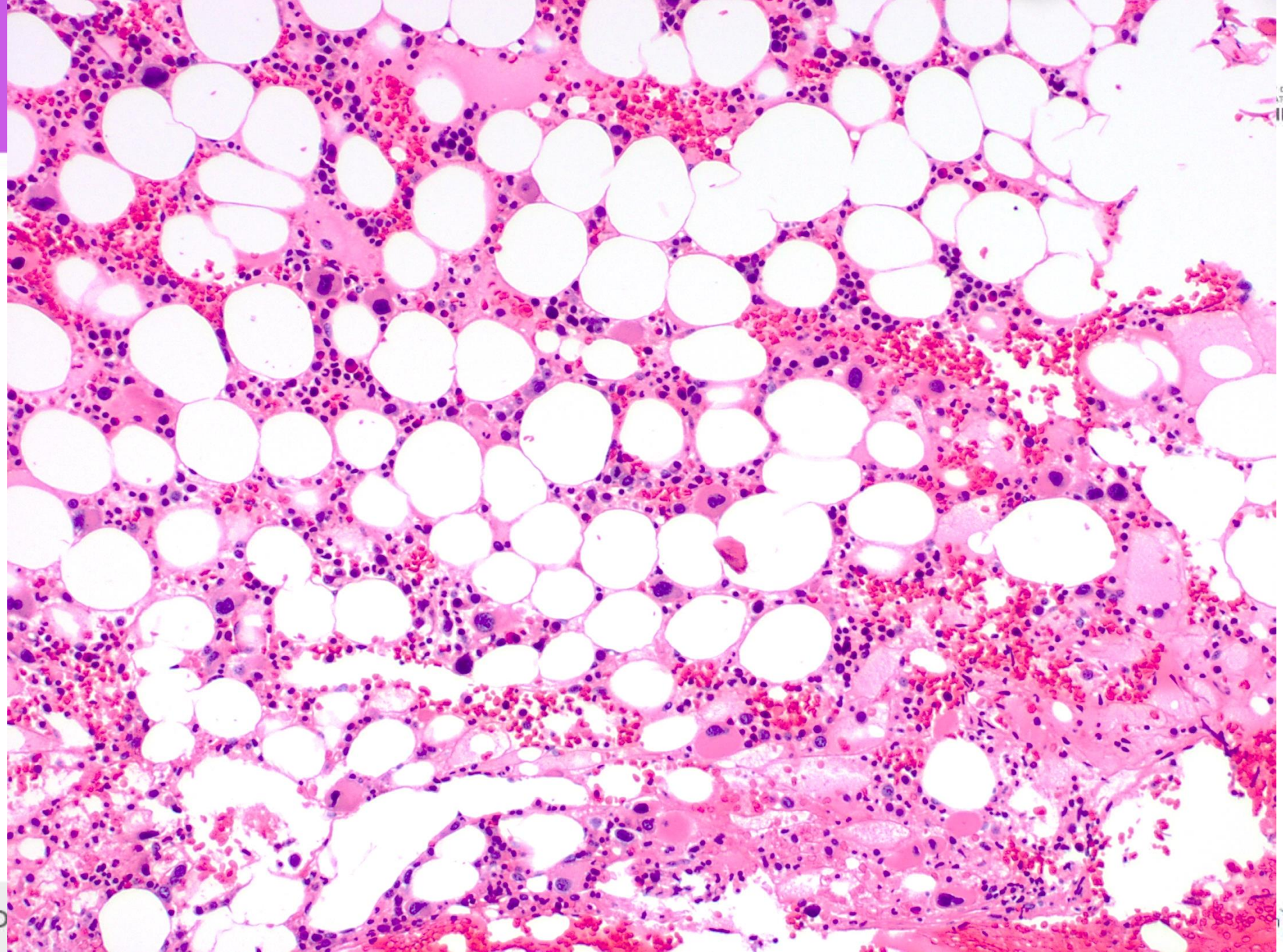
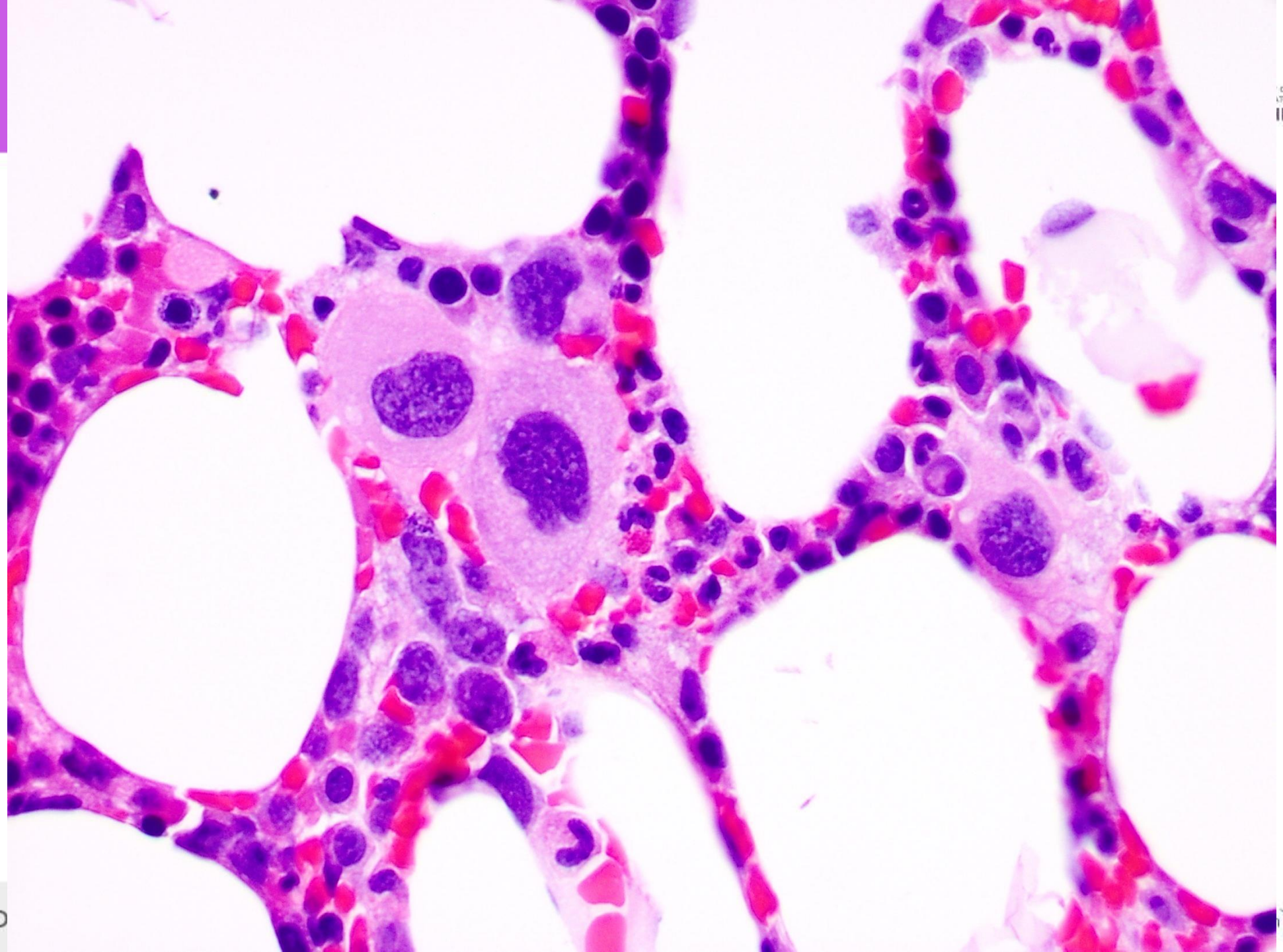
MDS WITH DEL(5Q)

MDS WITH LOW BLASTS AND ISOLATED 5Q DELETION

- The diagnostic criteria have not changed from WHO4
- Only applies in cases with low blast count (<5% bone marrow / <2% blood blasts)
- Most patients are elderly females who present with macrocytic anemia
    - About 1/3 of patients have thrombocytosis
- The bone marrow is normo or hypocellular with increased atypical megakaryocytes with characteristic morphology
- Cytogenetics allow presence of 5q deletion +/- 1 other abnormality (not del(7q) or monosomy 7)
- Presence of *SF3B1* (20%), *JAK2* (6%) or *TP53* (18%) mutation (except multi-hit) is acceptable
- Prognosis: good





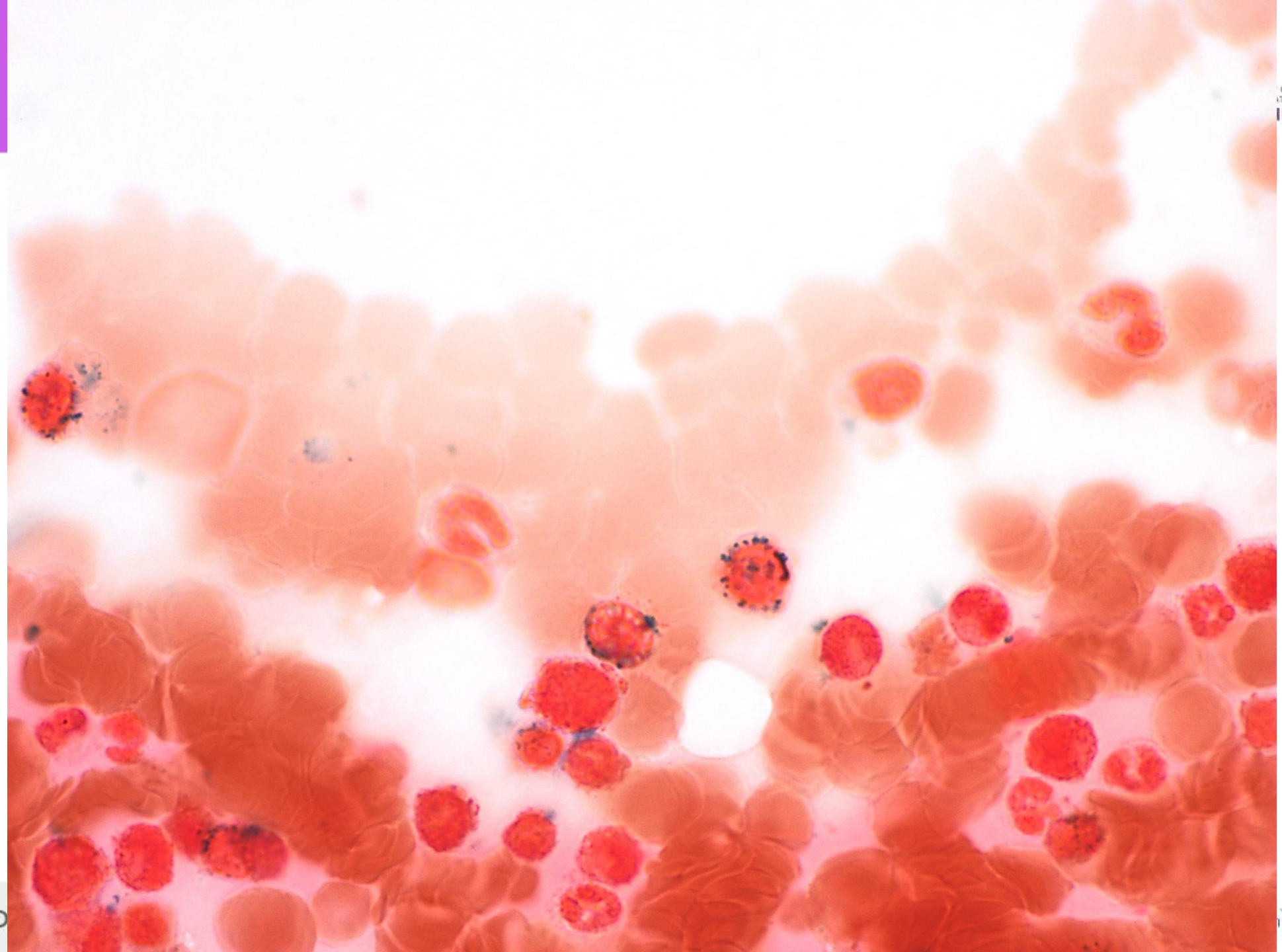
MDS WITH MUTATED *SF3B1*

MDS WITH LOW BLASTS AND *SF3B1* MUTATION

- Distinct MDS subtype that includes over 90% of MDS with ≥5% ring sideroblasts
- Ring sideroblasts are NOT required for diagnosis if *SF3B1* mutation is present
- Only applies in cases with low blast count (<5% bone marrow/<2% blood blasts)

  WHO: detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation if not available (WHO suggests the term " MDS with low blasts and ring sideroblasts")

  ICC : cases with ring sideroblasts but no *SF3B1* mutation are classified as MDS, NOS (regardless of the % ring sideroblasts)
- Cytogenetics: absence of del(5q), monosomy 7/del(7q), abnormal 3q or complex karyotype
- Mutations: SF3B1 with ≥10% VAF; absence of multi-hit TP53 or RUNX1
- Prognosis: very good



MDS WITH MUTATED *TP53*
MDS WITH BIALLELIC *TP53* INACTIVATON

- Multiple *TP53* hits (multi-hit)= biallelic *TP53* alteration = lacks residual wild-type p53 proteins
- About 10% of MDS patients have *TP53* abnormalities, among them ~2/3 are multi-hit alterations
- Detection requires gene sequencing, FISH and/or array techniques
- Immunohistochemical staining for p53 protein accumulation can be a valuable screening tool
    - Strong nuclear staining correlates with *TP53* mutations
    - Correlation with results of the molecular and cytogenetic studies is still needed to distinguish between a single hit and a multi-hit *TP53* alteration

MDS WITH TP53 ALTERATIONS

WHO:

- Myeloid neoplasm with cytopenia, dysplasia and <20% blasts or <30% erythroblasts
- Detection of ≥ 2 *TP53* mutations
- Detection of one mutation + *TP53* copy number loss
- Additional studies needed to determine if biallelic *TP53* is an AML defining event

ICC

- MDS with ≤9% bone marrow and peripheral blood blasts
- Detection of ≥ 2 *TP53* mutations (VAF ≥10%)
- Detection of one mutation associated with:
  - Cytogenetic deletion of *TP53* locus at chromosome 17p13.1
  - Copy-neutral loss of heterozygosity (LOH) at the 17p *TP53* locus
- If LOH information is not available, presence of a single *TP53* mutation + complex karyotype = equivalent to multi-hit *TP53*

MDS WITH TP53 ALTERATIONS

- Cytogenetics: >90% of patients have a complex karyotype
    - Complex karyotype with *TP53* deletion but no evidence of mutation does NOT qualify for this entity
- Mutations:
    - *TP53* VAF ≥50% may be considered presumptive evidence of LOH if a constitutional *TP53* variant can be ruled out
    - monoallelic *TP53* mutations appear to have a different biology and are NOT included in the entity
- Prognosis: terrible

62-year-old woman with worsening pancytopenia

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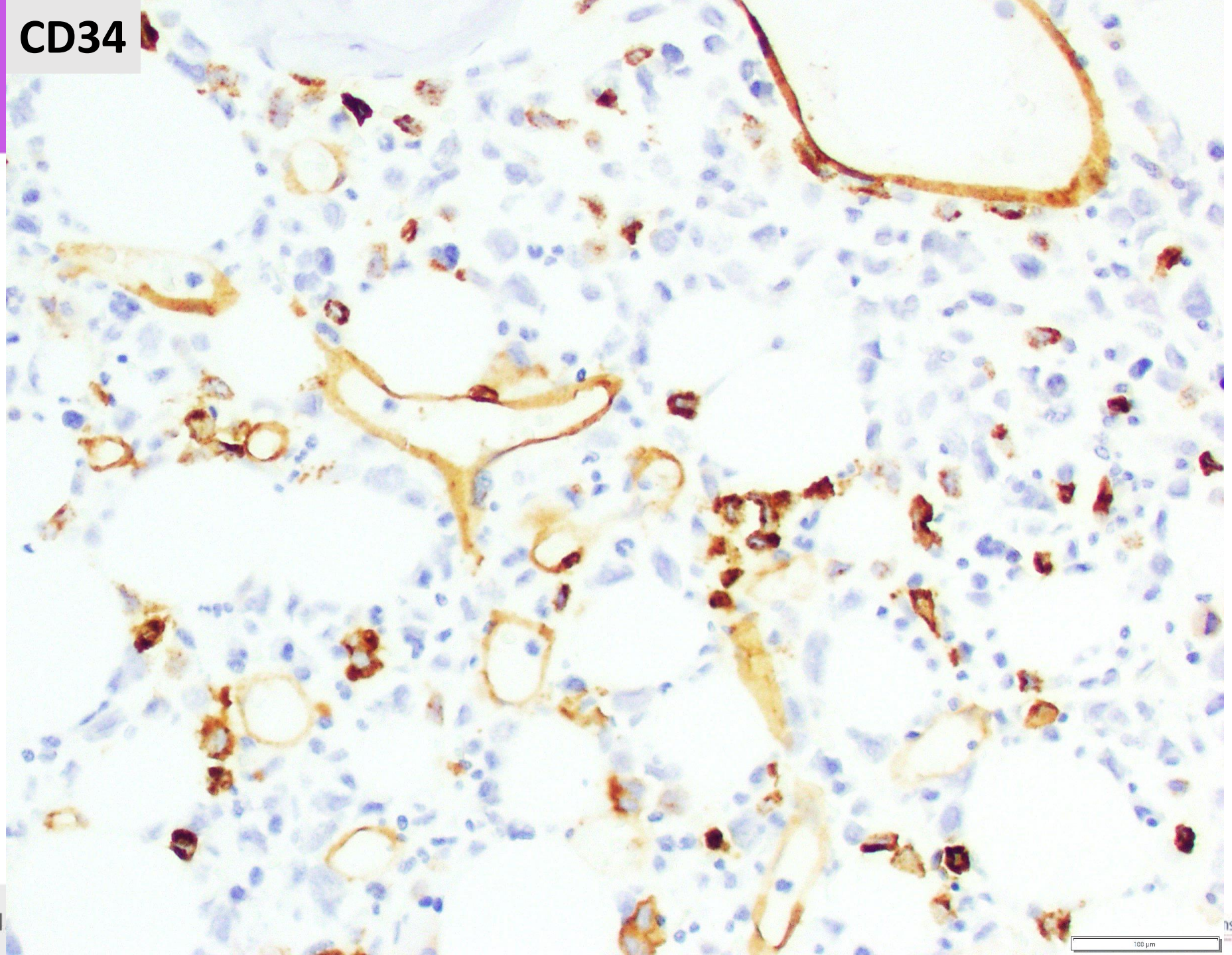
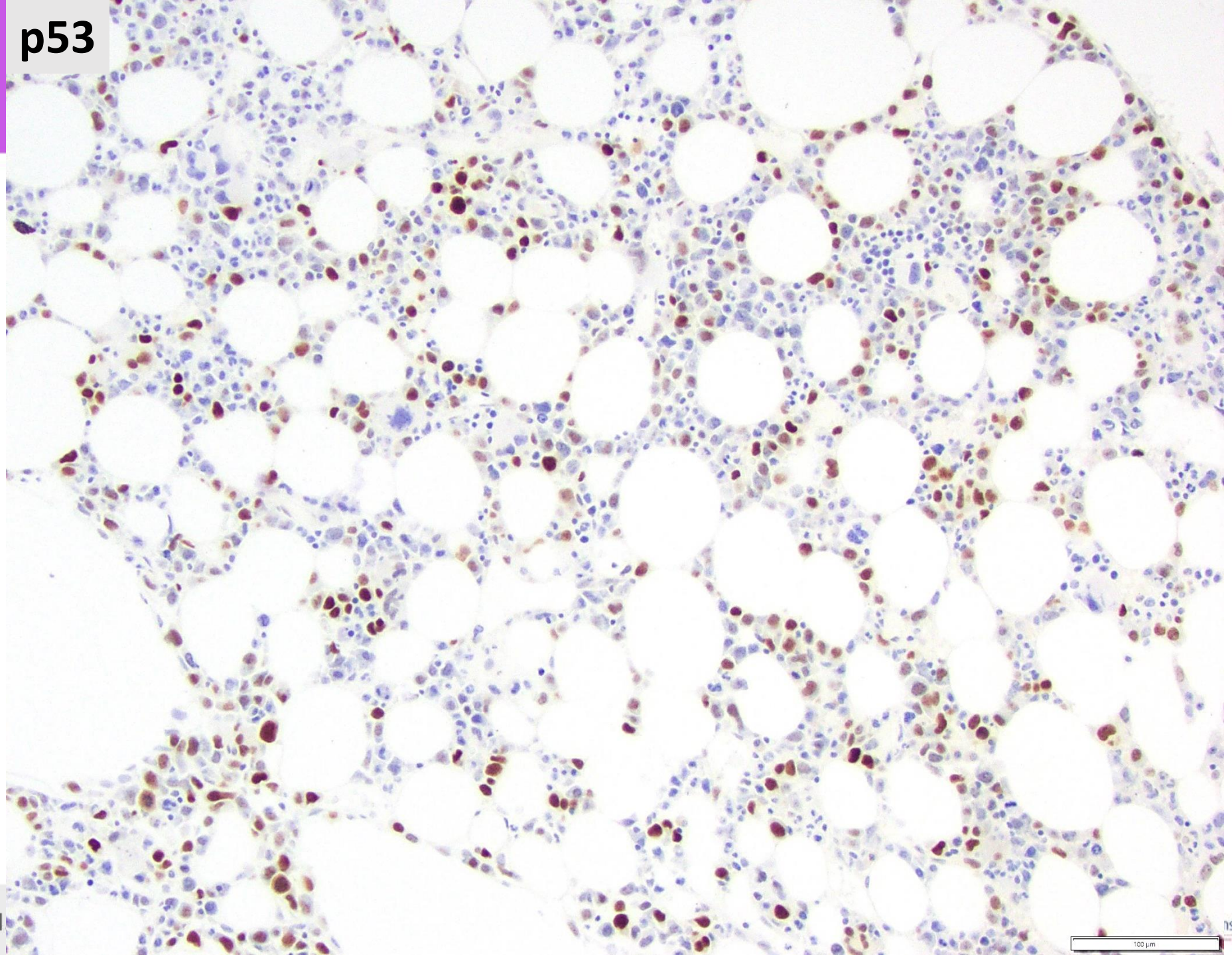


p53



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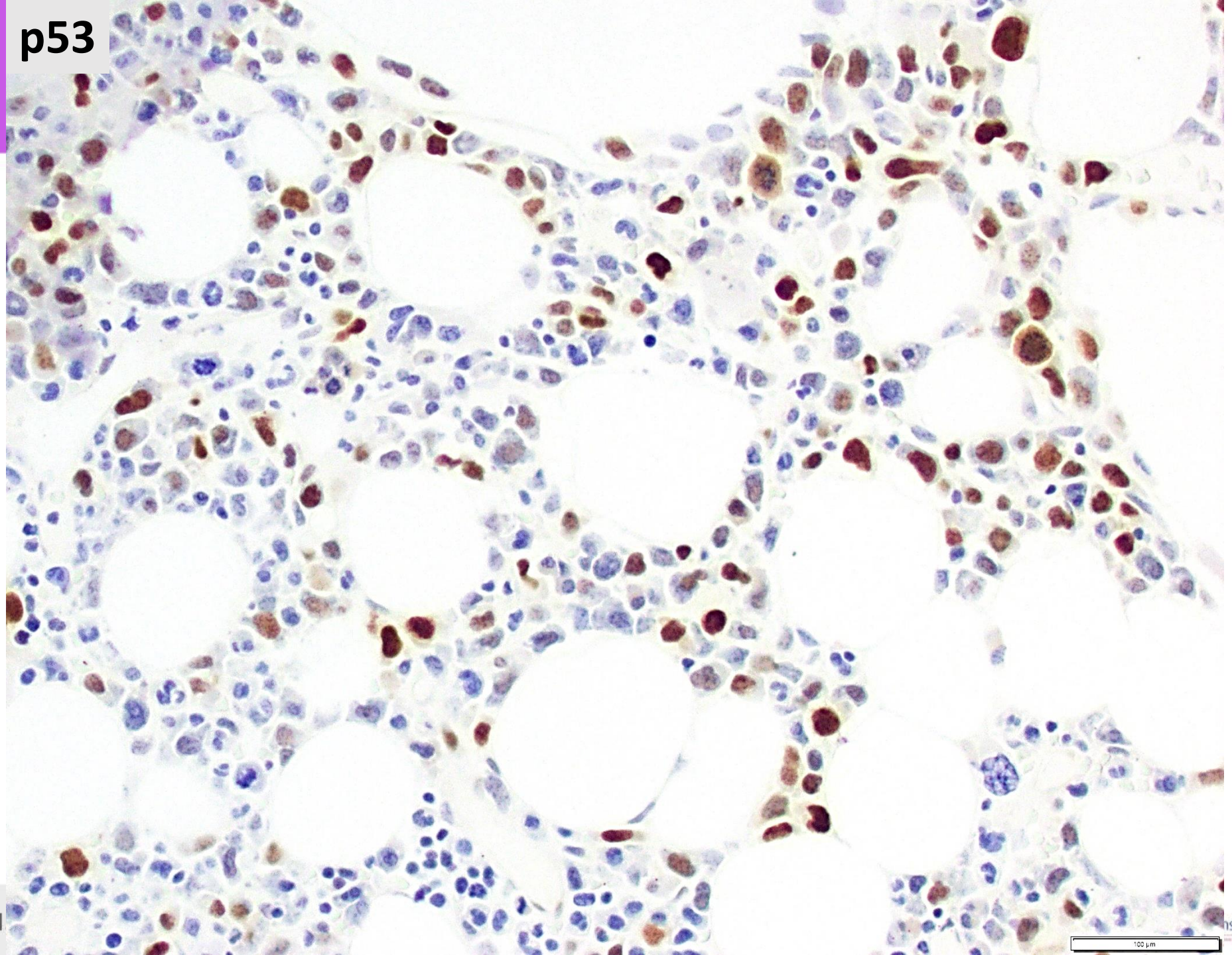
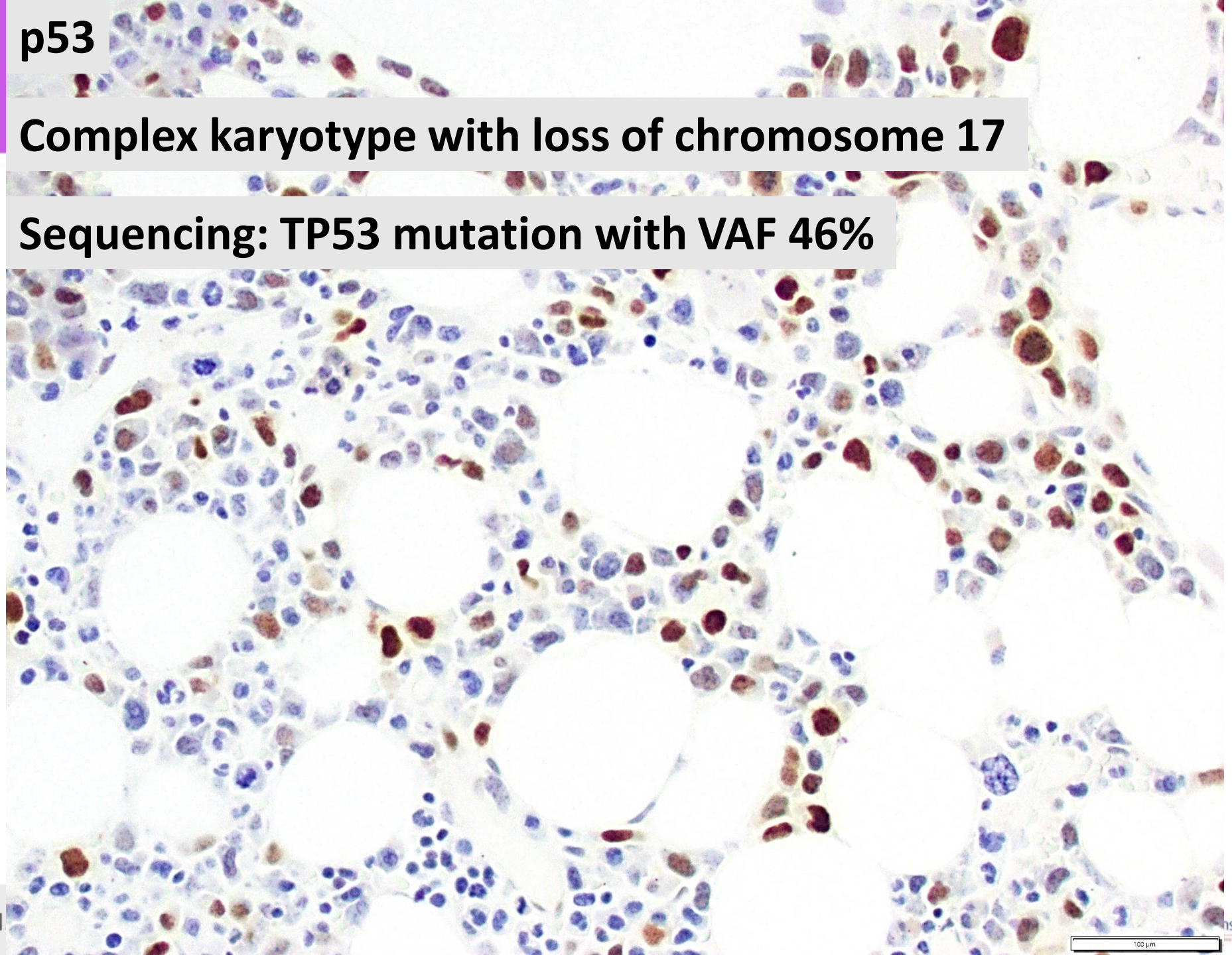
p53



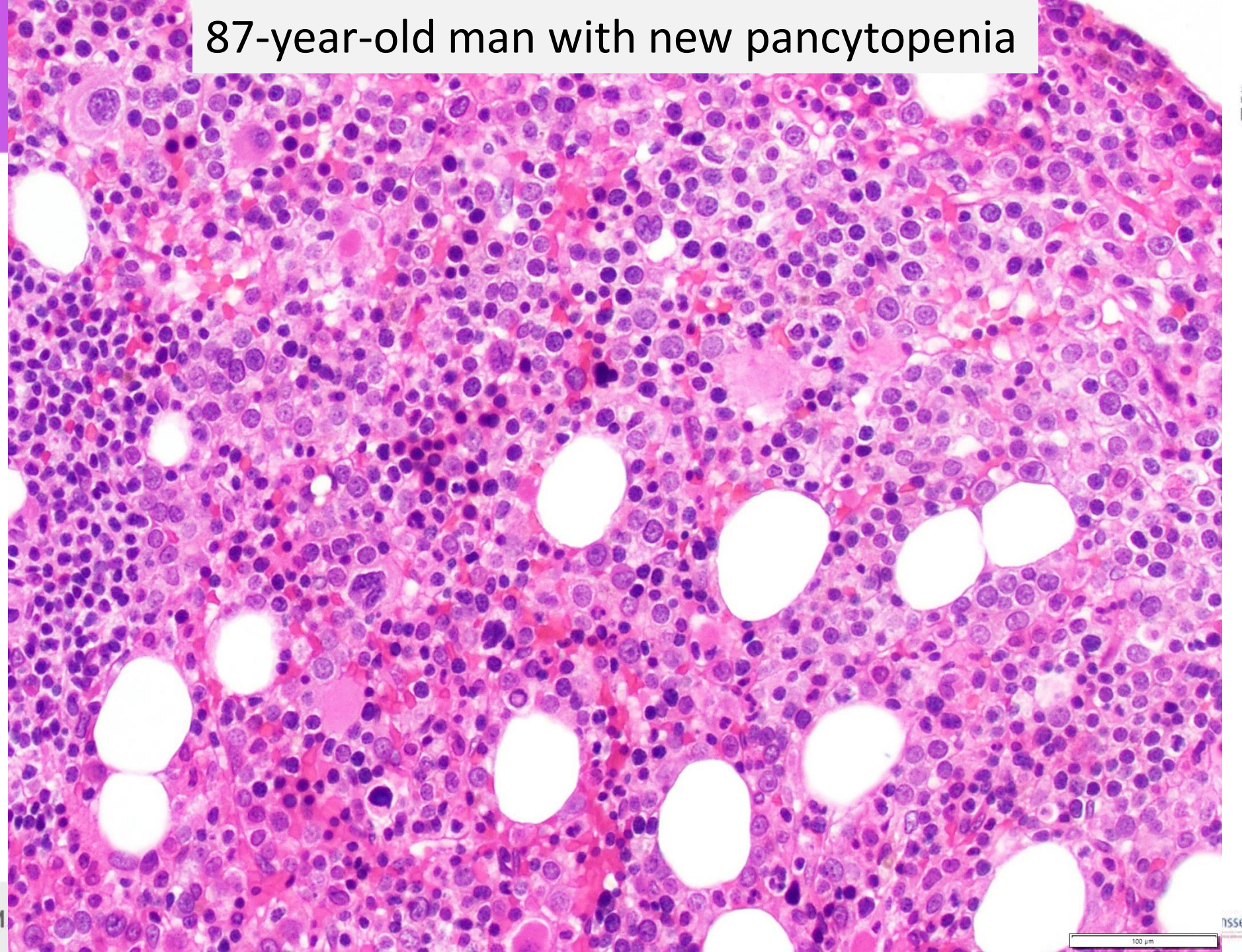
p53

Complex karyotype with loss of chromosome 17

Sequencing: TP53 mutation with VAF 46%



87-year-old man with new pancytopenia



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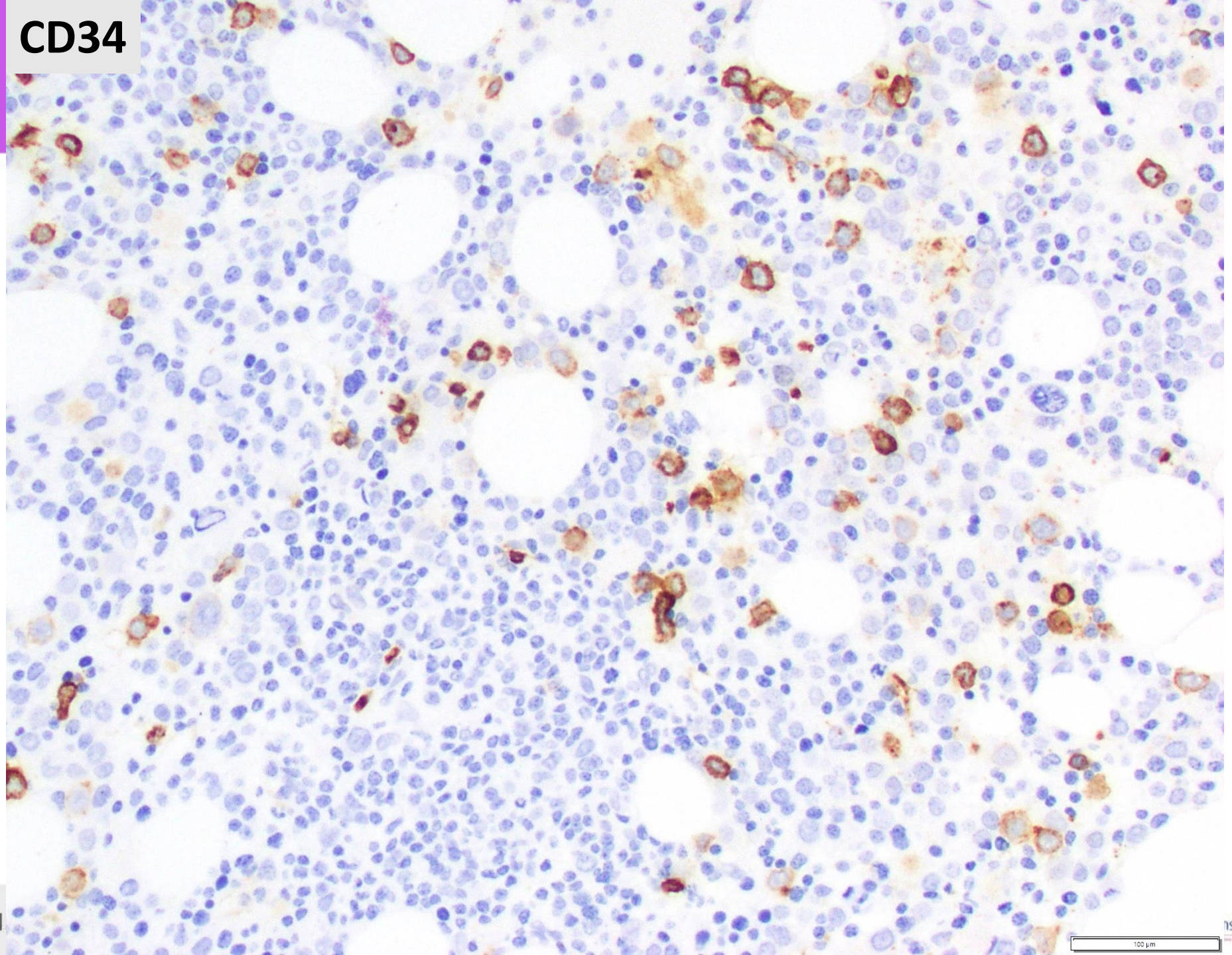
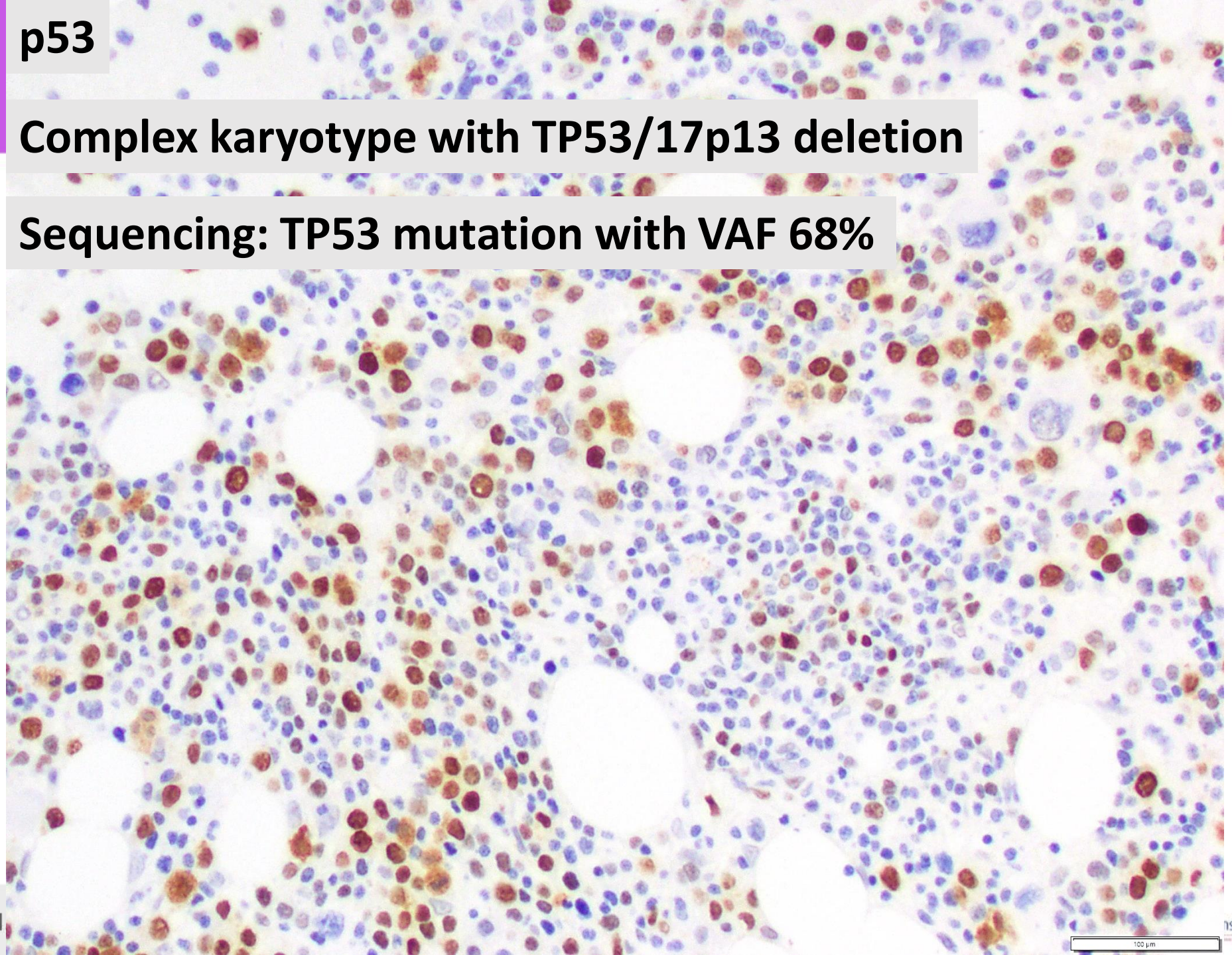


p53

Complex karyotype with TP53/17p13 deletion

Sequencing: TP53 mutation with VAF 68%



SPECIAL NOTE ON PRE-EXISTING CONDITIONS AND *TP53*

What happens if the patient has been exposed to cytotoxic agents? (~50% of patients with therapy-related myeloid neoplasms have *TP53* mutations)

What if the patient is known to have a germline *TP53* P/LP variant (Li-Fraumeni syndrome)?

WHO:

- New category of "Secondary Myeloid Neoplasms" supersedes "MDS with mutated *TP53*"
- Prior therapy→ "Myeloid Neoplasm post-Cytotoxic Therapy"
- Li-Fraumeni syndrome→ "Myeloid Neoplasm associated with Germline Predisposition"

ICC:

- "MDS with mutated *TP53*" and a diagnosis qualifier added (for example, "MDS with mutated TP53, therapy-related")

MDS, NOS
MDS WITH LOW BLASTS

Include cases of MDS with <5% bone marrow/<2% blood blasts

WHO:

- Myeloid neoplasm with cytopenia, dysplasia and low blasts
- Distinction between single lineage and multilineage dysplasia is optional
- Does not fulfil diagnostic criteria of MDS with defining genetic alterations or hypoplastic MDS
- Detection of clonal cytogenetic and/or molecular abnormality is desirable but not required

MDS, NOS
MDS WITH LOW BLASTS

Include cases of MDS with <5% bone marrow/<2% blood blasts

ICC: includes 3 subtypes

- MDS, NOS without dysplasia (rare)
  - Defined by presence of monosomy7/de(7q) or complex karyotype
  - All other MDS-defining abnormalities (WHO4) in patients with cytopenia but no dysplasia are now reclassified as CCUS
- MDS, NOS with single lineage dysplasia
- MDS, NOS with multilineage dysplasia

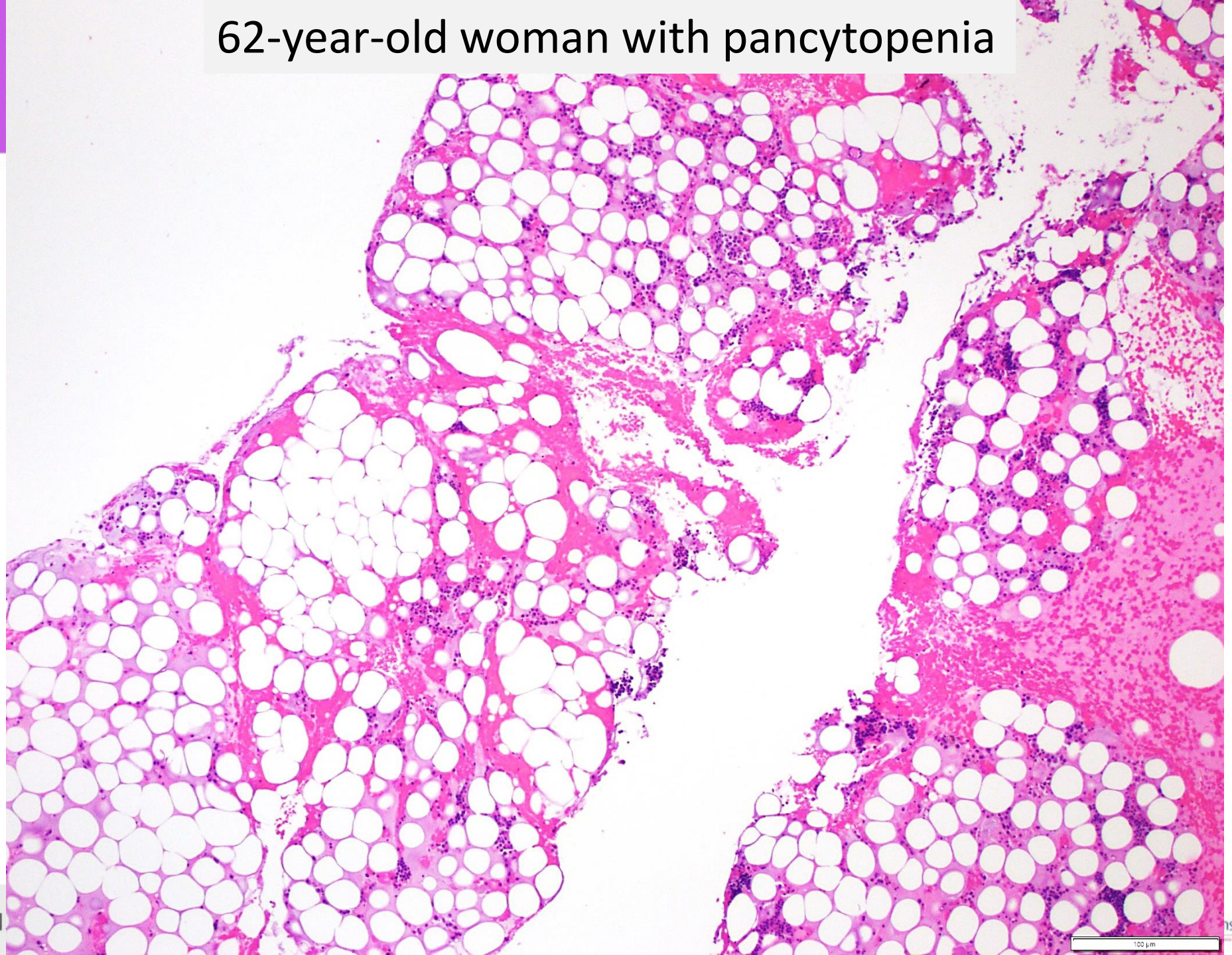
MDS, HYPOPLASTIC

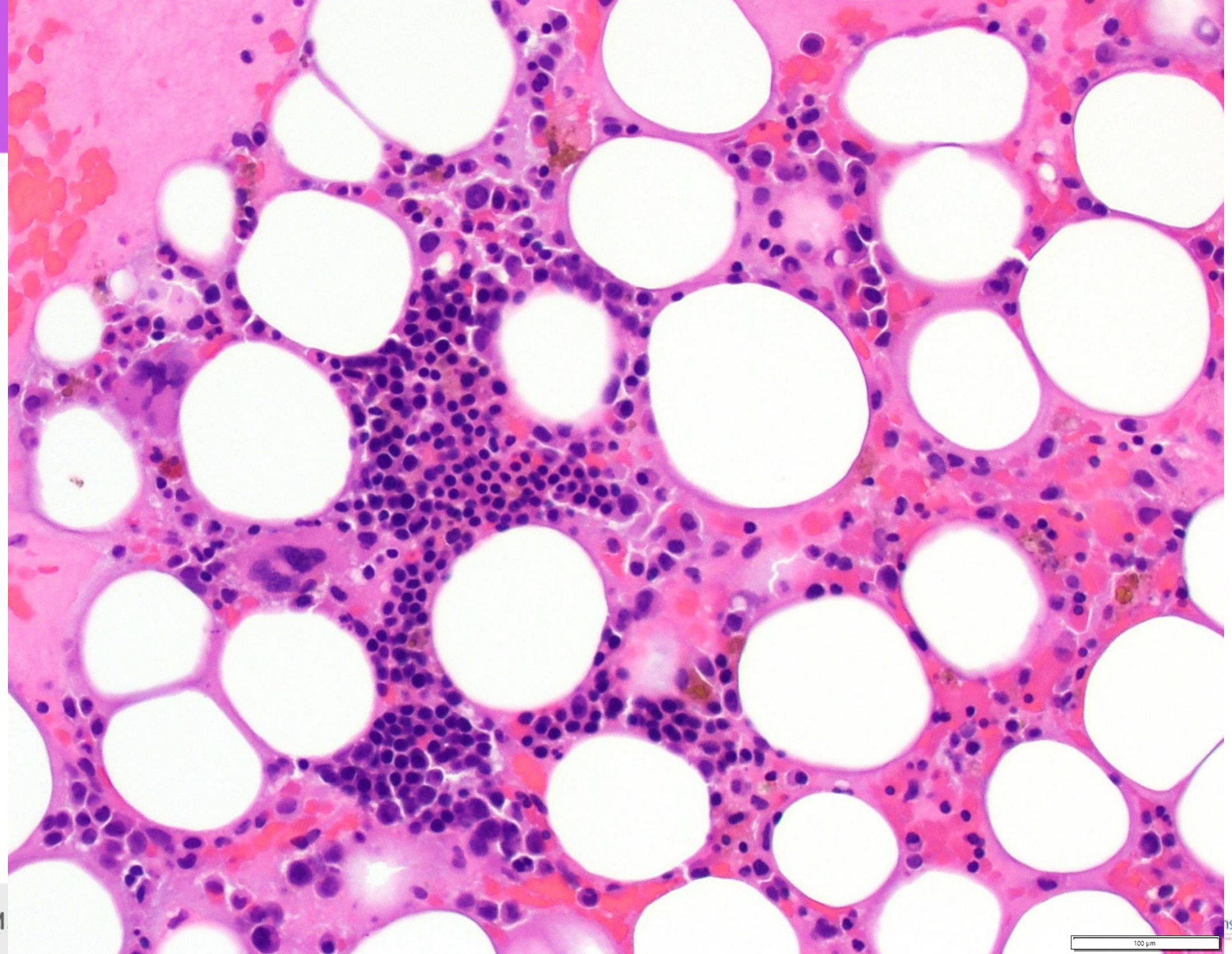
- New category in the WHO
- Defined as myeloid neoplasm with cytopenia and dysplasia, characterized by significantly decreased age-adjusted bone marrow cellularity as determined on a trephine biopsy
- Represent ~10-15% of all MDS
- Patients are usually younger than those with other MDS types but older than those with aplastic anemia
- Hypoplasia may be driven by a T-cell mediated immune attack on hematopoietic stem cells with oligoclonal expansion of CD8+ T-cells overproducing IFNγ and/or TNFα
- Significant overlap with paroxysmal nocturnal hemoglobinuria (PNH) and aplastic anemia (AA) is reported
- Patients with germline mutations of *GATA2*, *DDX41*, Fanconi anemia or telomerase complex genes can have hypoplastic bone marrows and evolve to MDS

MDS, HYPOPLASTIC

- Bone marrow cellularity must be significantly decreased
  - <30% of normal cellularity in patients younger than 70 years
  - <20% in patients aged 70 and older
- Blast counts are variable and clustering of blasts on trephine biopsy may be observed
- Not meeting criteria for MDS with defining genetic abnormalities or MDS with increased blasts
- Cytogenetics: chromosomal abnormalities are detected in 25-40% of cases
- Mutations: there is a lower prevalence of somatic mutations compared to other MDS types
- Prognosis: good likely due to favorable response to immunosuppressive therapy

62-year-old woman with pancytopenia





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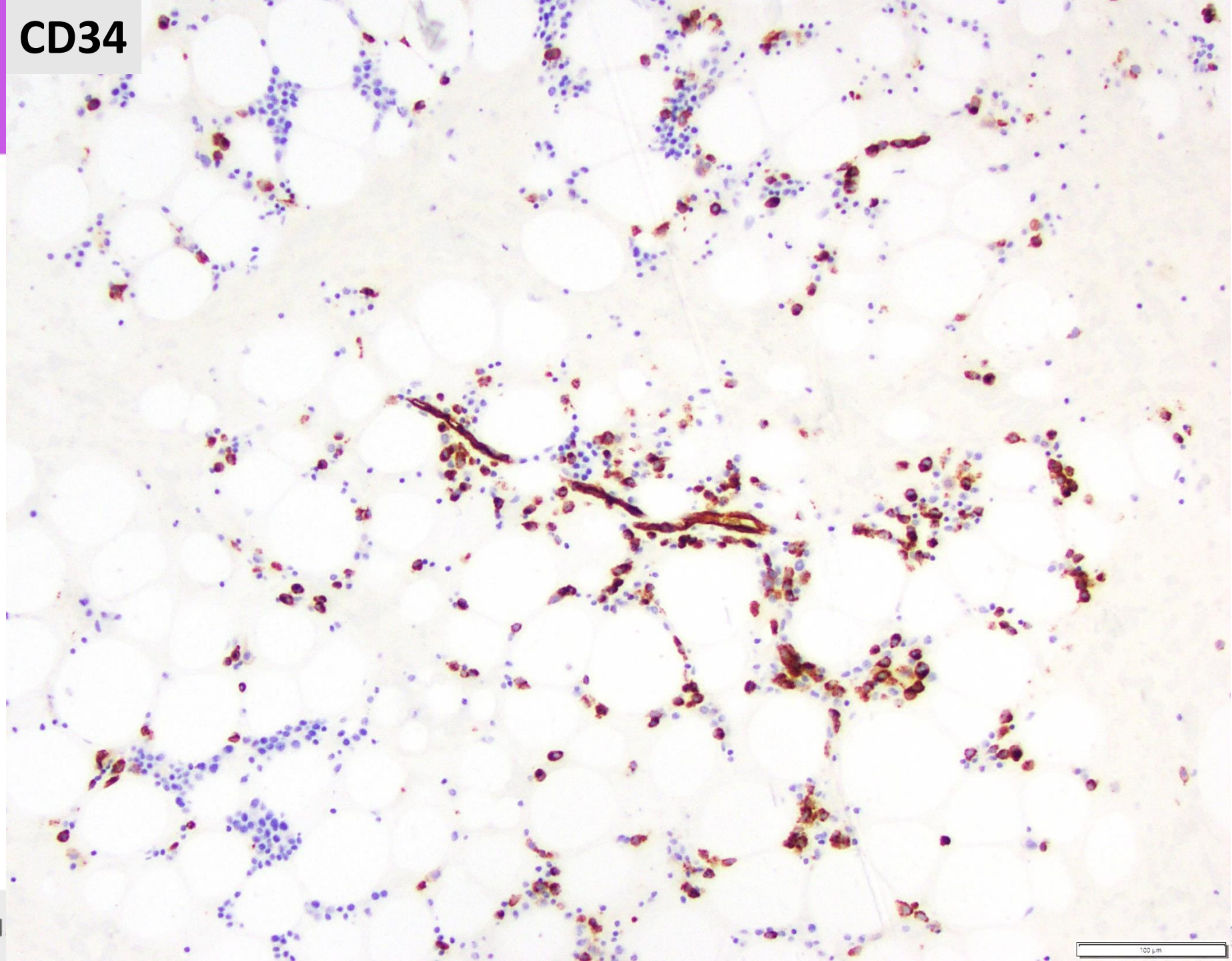
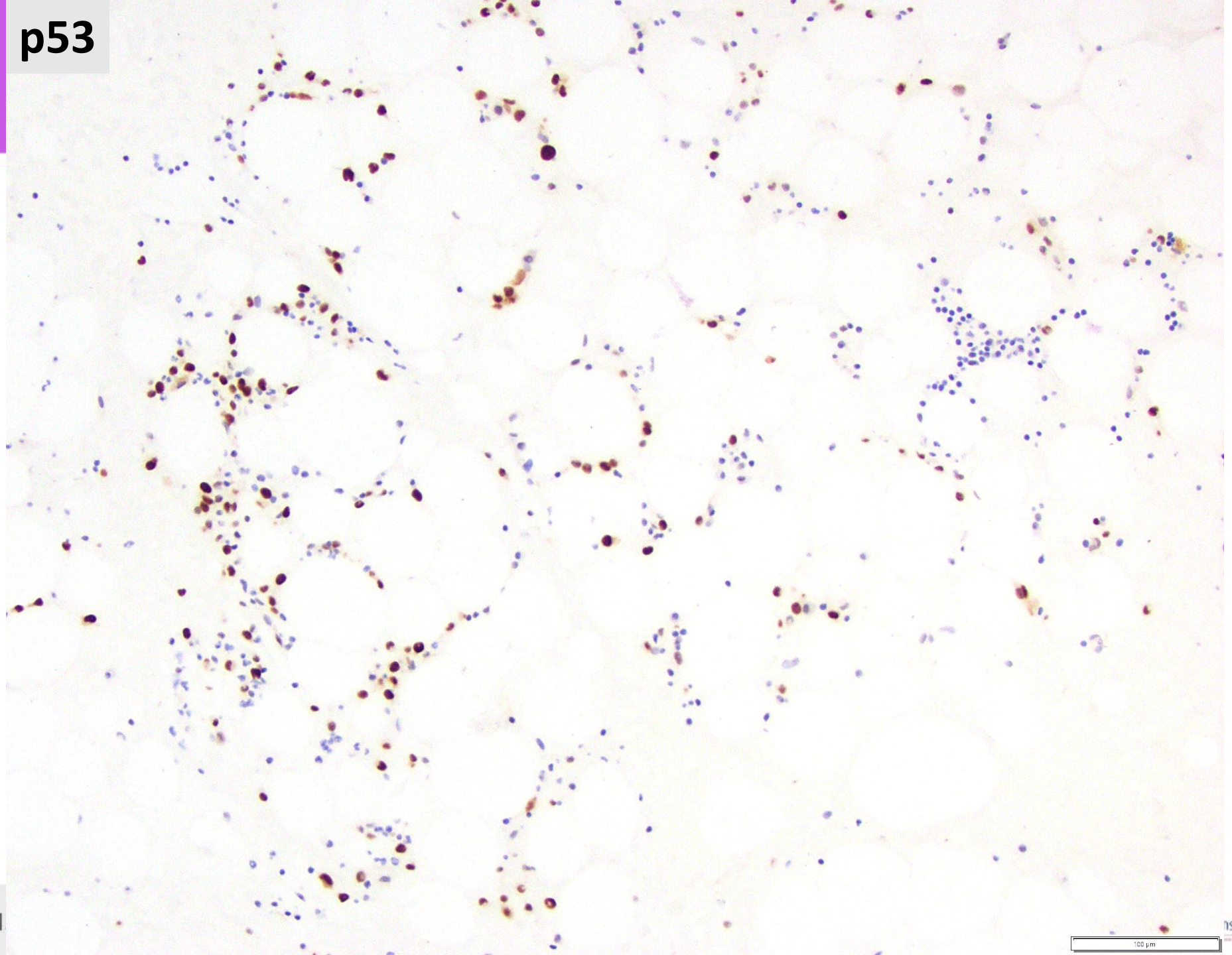


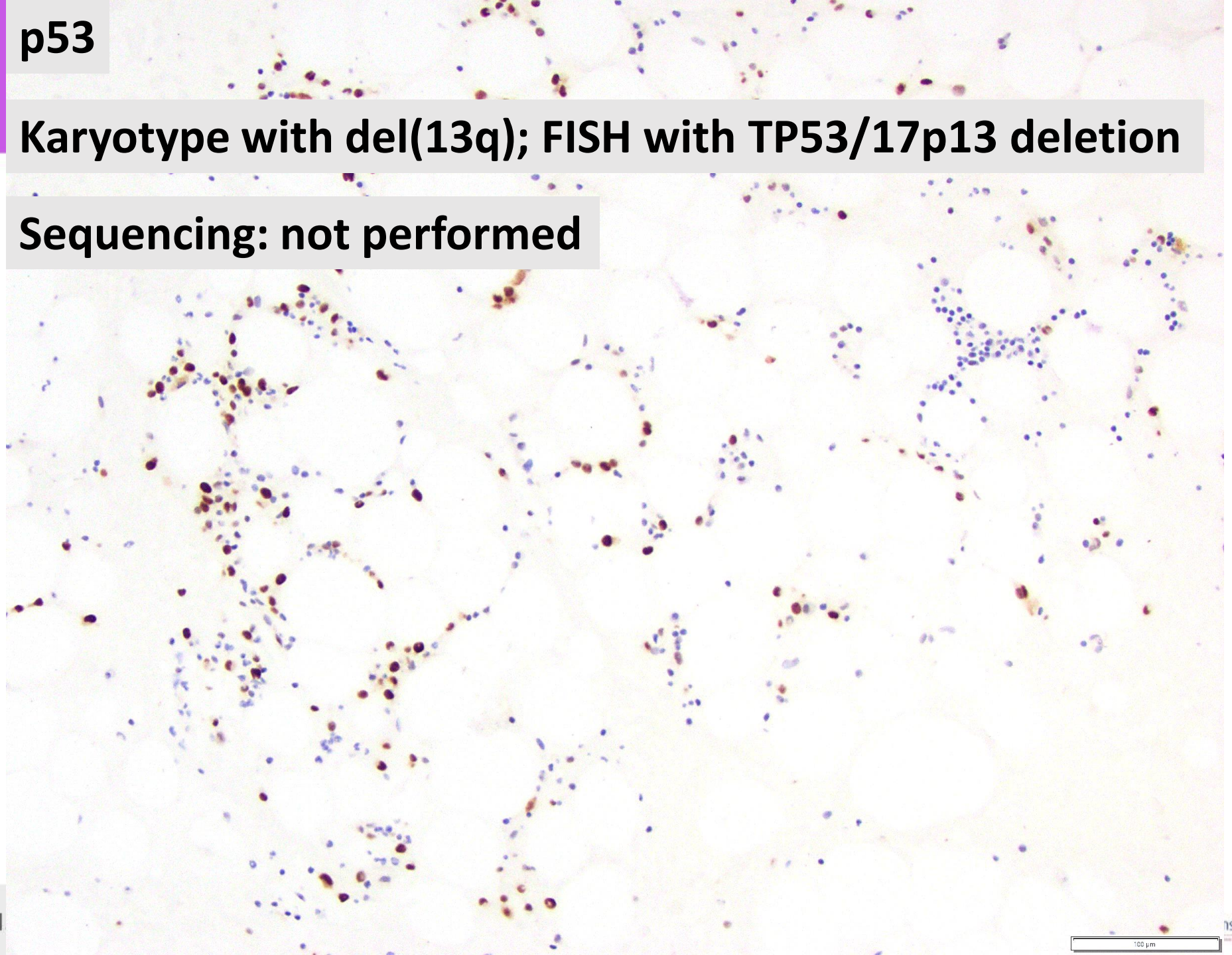
p53



p53

Karyotype with del(13q); FISH with TP53/17p13 deletion

Sequencing: not performed



MDS WITH EXCESS BLASTS (MDS-EB)
MDS WITH INCREASED BLASTS (MDS-IB1)

WHO: MDS with increased blasts is divided into IB1 and IB2

- IB1 = 5-9% bone marrow blasts or 2-4% peripheral blood blasts
- IB2 = 10-19% bone marrow blasts or 5-19% peripheral blood blasts
- Not fulfilling diagnostic criteria of MDS with biallelic *TP53* inactivation or AML

ICC :

- MDS-EB = 5-9% bone marrow blasts or 2-9% peripheral blood blasts (or Auer rods)
- Excluded if multi-hit *TP53* mutations are present

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MDS WITH INCREASED BLASTS (MDS-IB2)

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- IB2 = 10-19% bone marrow blasts or 5-19% peripheral blood blasts
- Not fulfilling diagnostic criteria of MDS with biallelic *TP53* inactivation or AML

  - "the pros and cons of merging MDS-IB2 with AML were explored in multidisciplinary expert discussions and at editorial board meetings…. an arbitrary cut-off of 10% blasts to define AML carries a risk of overtreatment"
  - "broad agreement that MDS-IB2 may be regarded as AML-equivalent for therapeutic consideration and from a clinical trial design perspective"

Khoury JD et al. Leukemia 2022

MDS / AML

MDS WITH INCREASED BLASTS (MDS-IB2)

ICC:

- MDS/AML = 10-19% bone marrow or peripheral blood blasts
- Excluded if AML-defining recurrent cytogenetic abnormalities are present*
- Excluded if *NPM1, bZIP CEBPA* or *TP53* mutations are present*
- The entity does not apply in pediatric (<18 years old) patients
  - "To acknowledge the biologic continuum between MDS and AML, the name…MDS-EB2 in adults with 10% of more blasts is changed to MDS/AML"
  - "Patients with MDS/AML should be eligible for both MDS and AML trials, which will facilitate optimizing the management of such patients"

*21 cytogenetic/molecular subtypes has been delineated!

Arber DA et al. Blood 2022

MDS / AML WITH MUTATED *TP53*

- Patients with 10-19% bone marrow or peripheral blood blasts
- Presence of ANY somatic *TP53* mutation with VAF >10%
    - Mono-allelic mutated *TP53* AML has poor prognosis

CLINICAL EXAMPLE 1

58-year-old woman with significant anemia, trilineage dysplasia, presence of 16% myeloid blasts, 17p deletion detected by FISH analysis and *TP53* mutation (VAF 30%)

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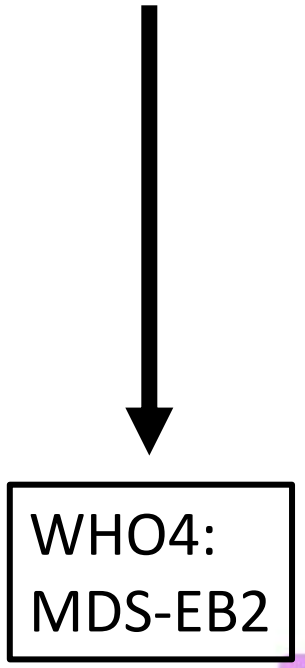

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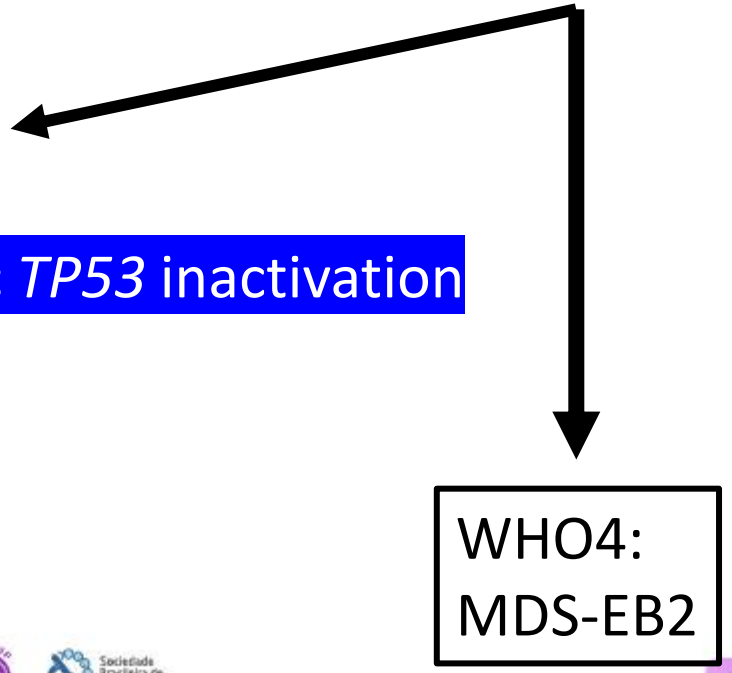

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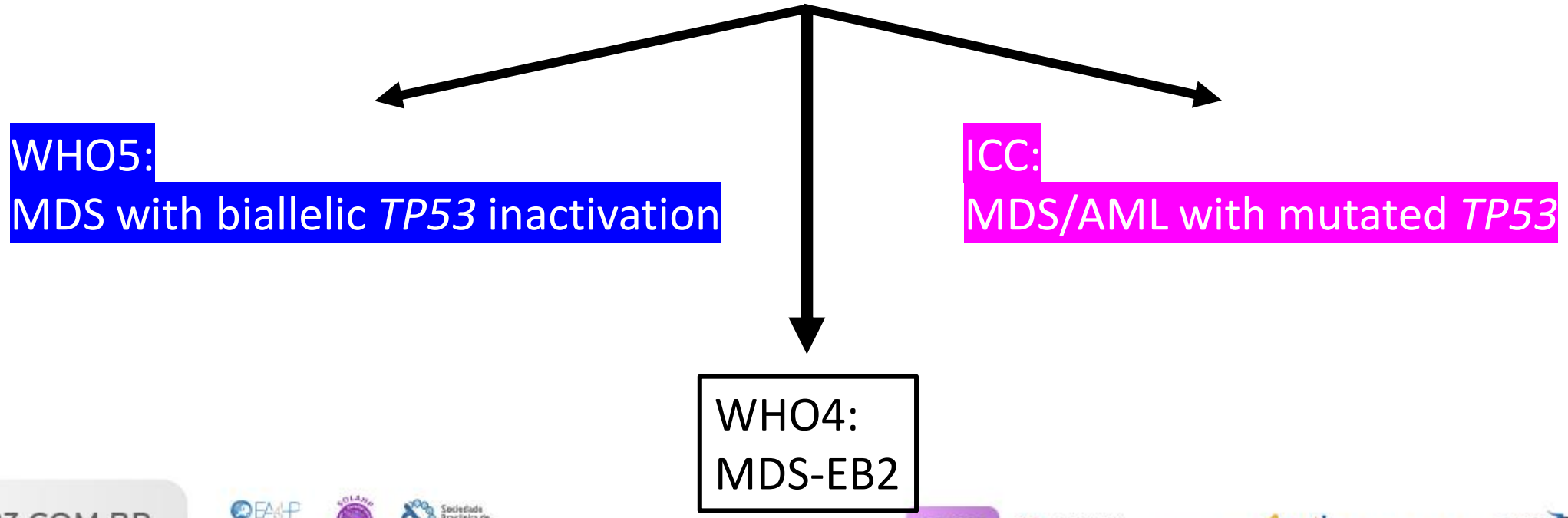

CLINICAL EXAMPLE 2

58-year-old woman with significant anemia, trilineage dysplasia, presence of 16% myeloid blasts, karyotype with trisomy 8 (+8) and *TP53* mutation (VAF 30%)

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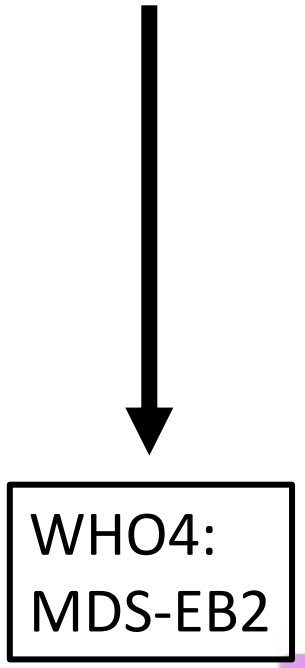

CLINICAL EXAMPLE 2

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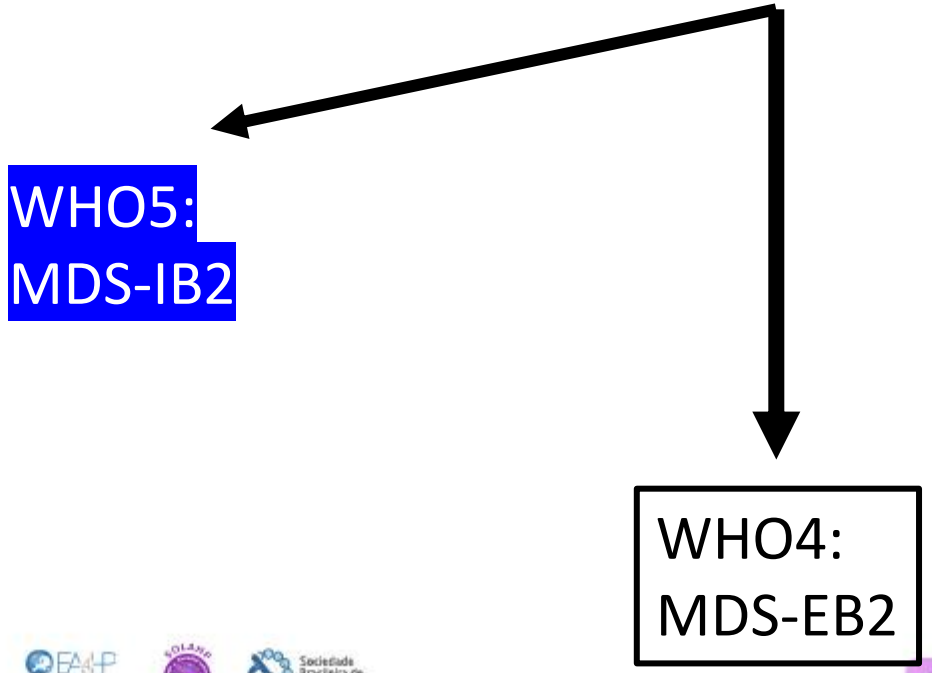
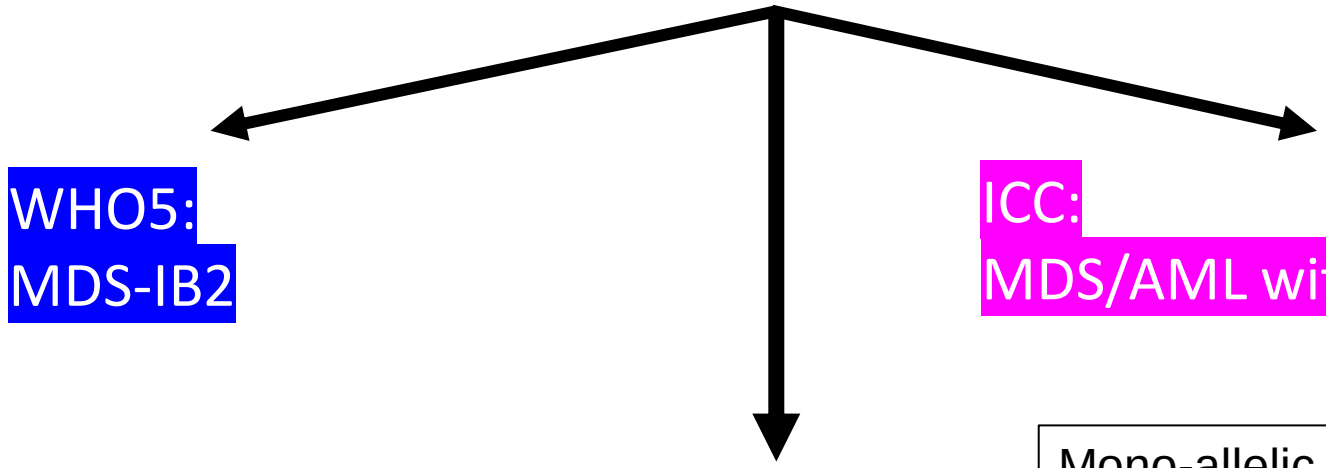


~1/3 of MDS-IB patients have mono-allelic *TP53* mutations whose clinical outcomes do not appear to differ from those with wild-type *TP53*

Bernard E, et al. Nature Med 2020

CLINICAL EXAMPLE 2

58-year-old woman with significant anemia, trilineage dysplasia, presence of 16% myeloid blasts, karyotype with trisomy 8 (+8) and *TP53* mutation (VAF 30%)



Mono-allelic mutated *TP53* AML has poor prognosis, thus mono-allelic mutations are allowed in MDS/AML and AML

Grob T, et al. Blood 2022

CLINICAL EXAMPLE 3

62-year-old man with significant anemia, presence of 16% ring sideroblasts, no increase in blasts, karyotype with trisomy 8 (+8) and *SF3B1* mutation (VAF 30%)

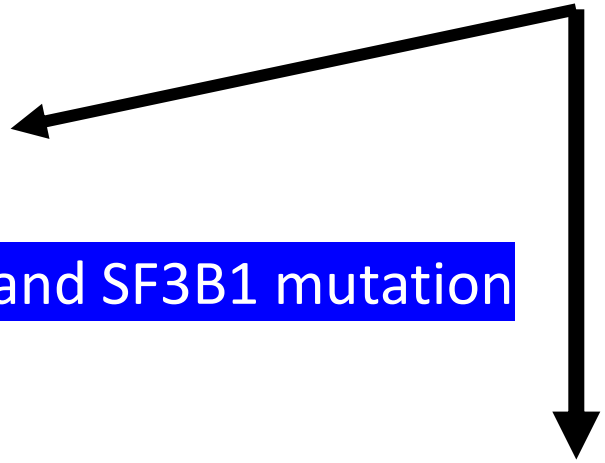
CLINICAL EXAMPLE 3

62-year-old man with significant anemia, presence of 16% ring sideroblasts, no increase in blasts, karyotype with trisomy 8 (+8) and *SF3B1* mutation (VAF 30%)

WHO4:
MDS with ring sideroblasts

CLINICAL EXAMPLE 3

62-year-old man with significant anemia, presence of 16% ring sideroblasts, no increase in blasts, karyotype with trisomy 8 (+8) and *SF3B1* mutation (VAF 30%)

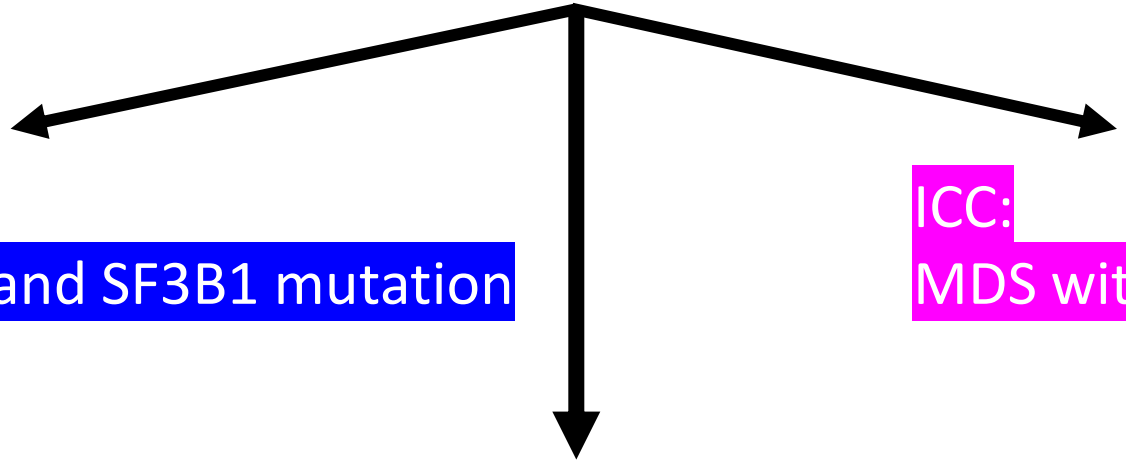


WHO5:
MDS with low blasts and SF3B1 mutation

WHO4:
MDS with ring sideroblasts

CLINICAL EXAMPLE 3

62-year-old man with significant anemia, presence of 16% ring sideroblasts, no increase in blasts, karyotype with trisomy 8 (+8) and *SF3B1* mutation (VAF 30%)



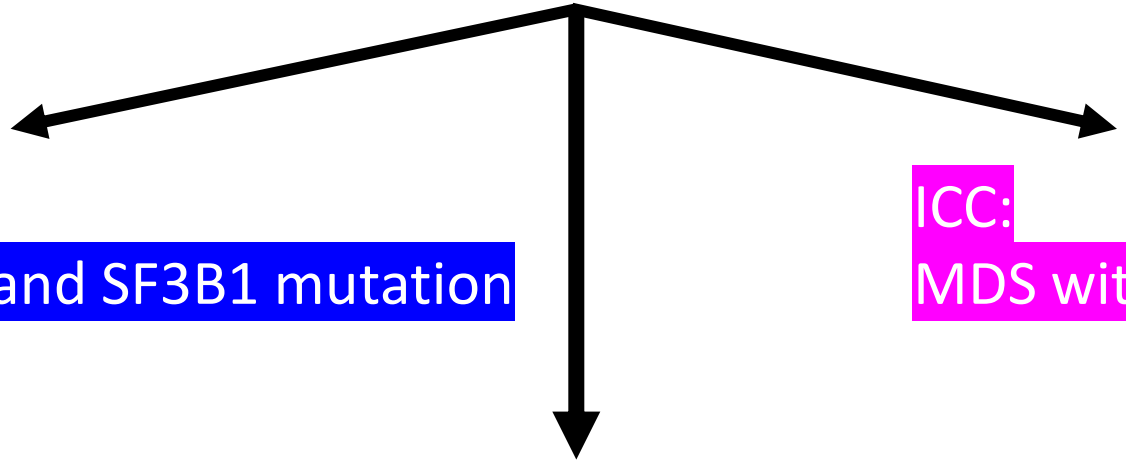
WHO5:
MDS with low blasts and SF3B1 mutation

ICC:
MDS with mutated *SF3B1*

WHO4:
MDS with ring sideroblasts

CLINICAL EXAMPLE 3

62-year-old man with significant anemia, presence of 16% ring sideroblasts, no increase in blasts, karyotype with trisomy 8 (+8) and *SF3B1* mutation (VAF 30%)



WHO5:
MDS with low blasts and SF3B1 mutation

ICC:
MDS with mutated *SF3B1*

WHO4:
MDS with ring sideroblasts

3° CONGRESO
LATINOAMERICANO DE
HEMATOPATOLOGÍA
SÃO PAULO | 2023

REALIZACIÓN

SOLAHP Sociedad Latinoamericana de Hematopatología

Sociedade Brasileira de PATOLOGIA

EA4HP European Association for Haematopathology

APOYO

RECORDATI RARE DISEASES GROUP

AstraZeneca

NOVARTIS

Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

A.C.Camargo Cancer Center Especializado em Vida

Agilent Dako