Sistema Socio Sanitario

Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ATS Pavia

GRAND ROUNDS CLINICI DEL MERCOLEDÌ

con il Policlinico San Matteo

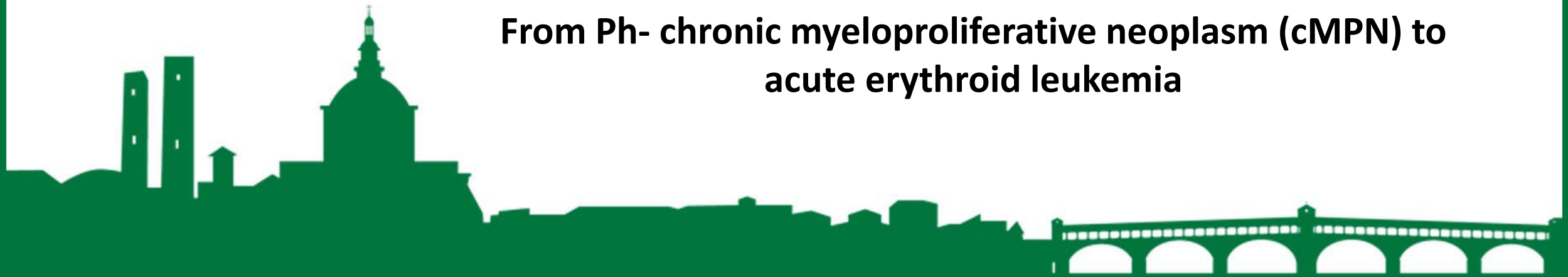
Aula Magna "C. Golgi" & WEBINAR

14 Febbraio 2024

Emanuela Boveri

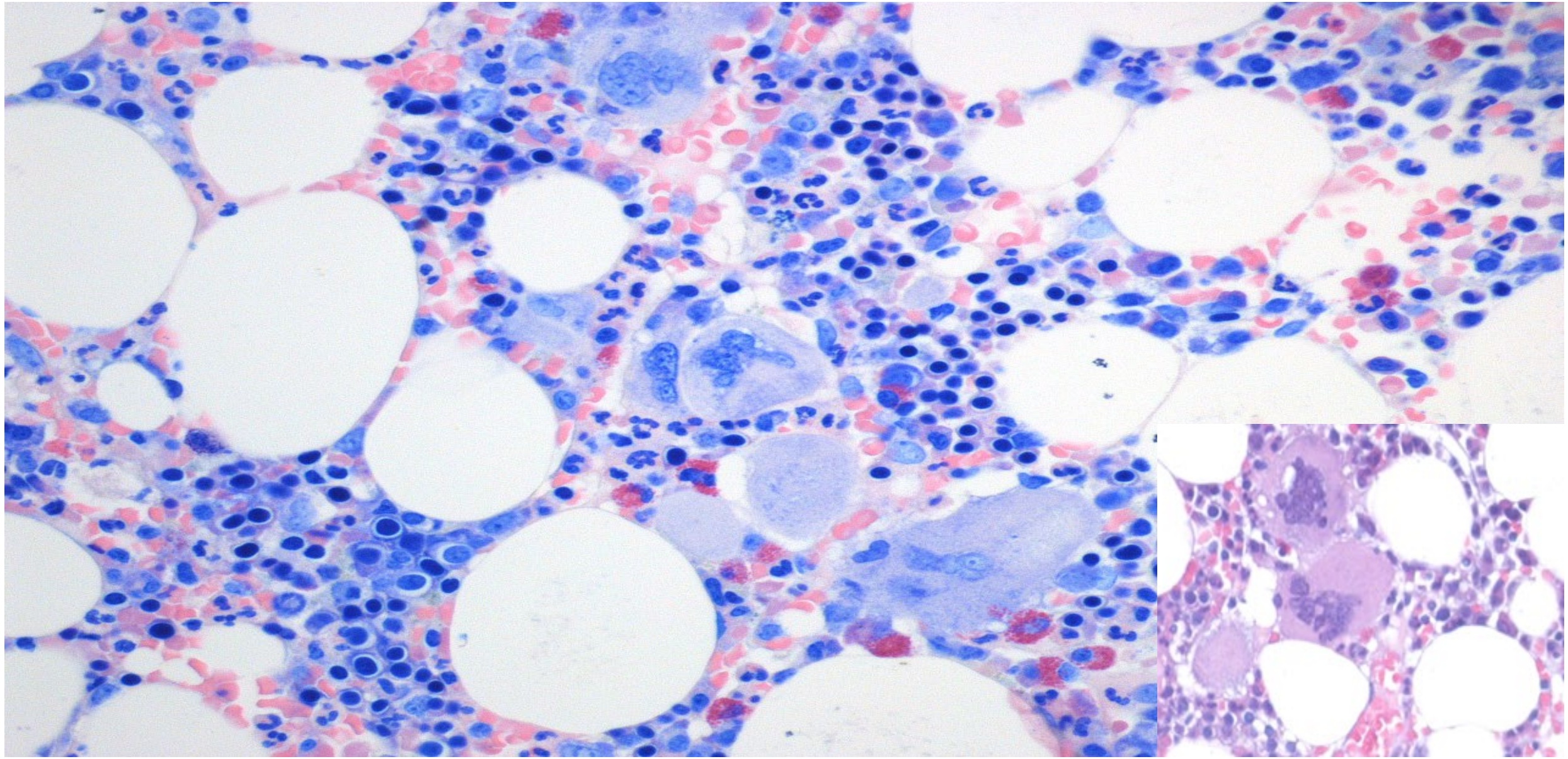
SC Anatomia Patologica

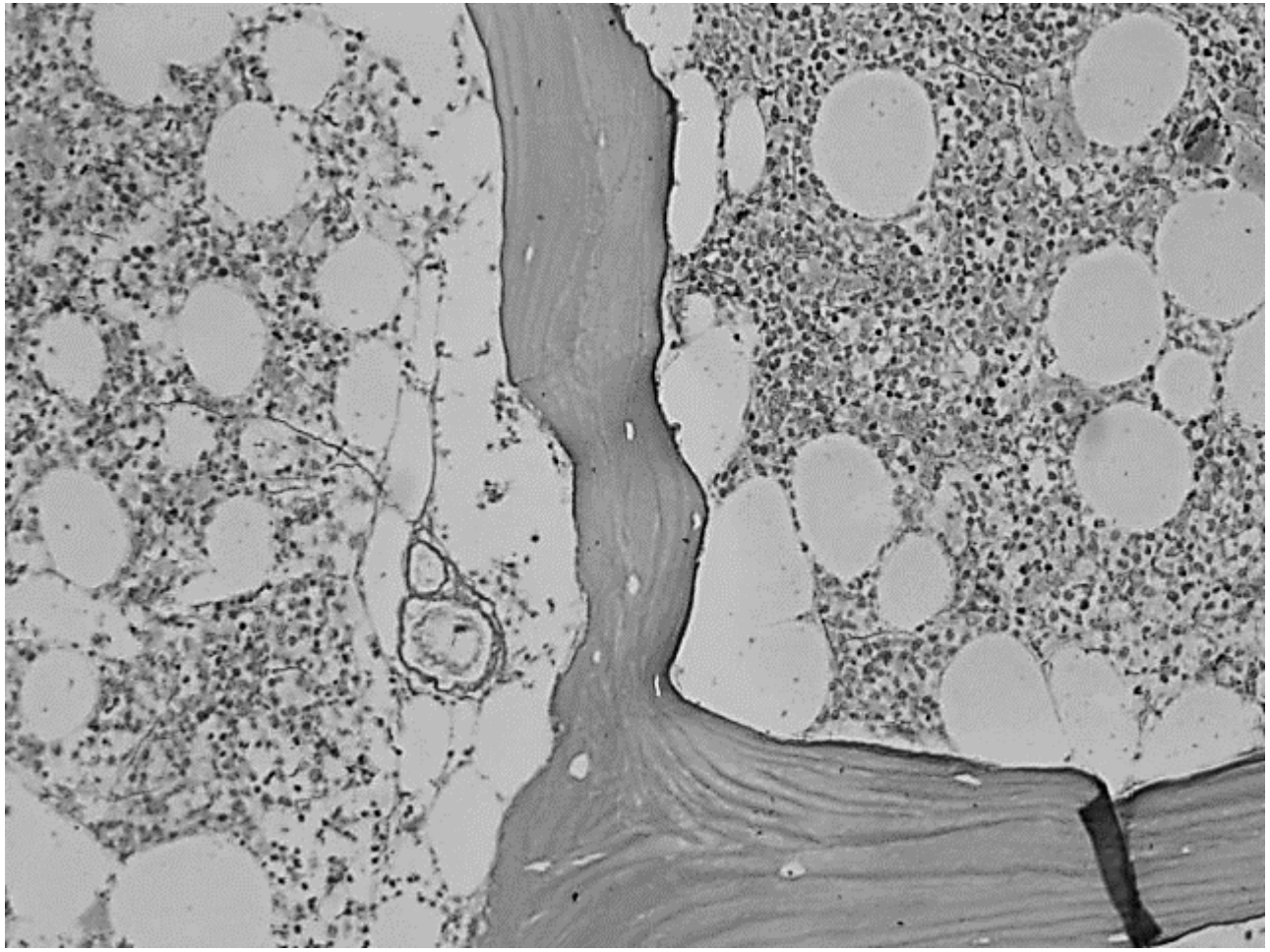
From Ph- chronic myeloproliferative neoplasm (cMPN) to acute erythroid leukemia

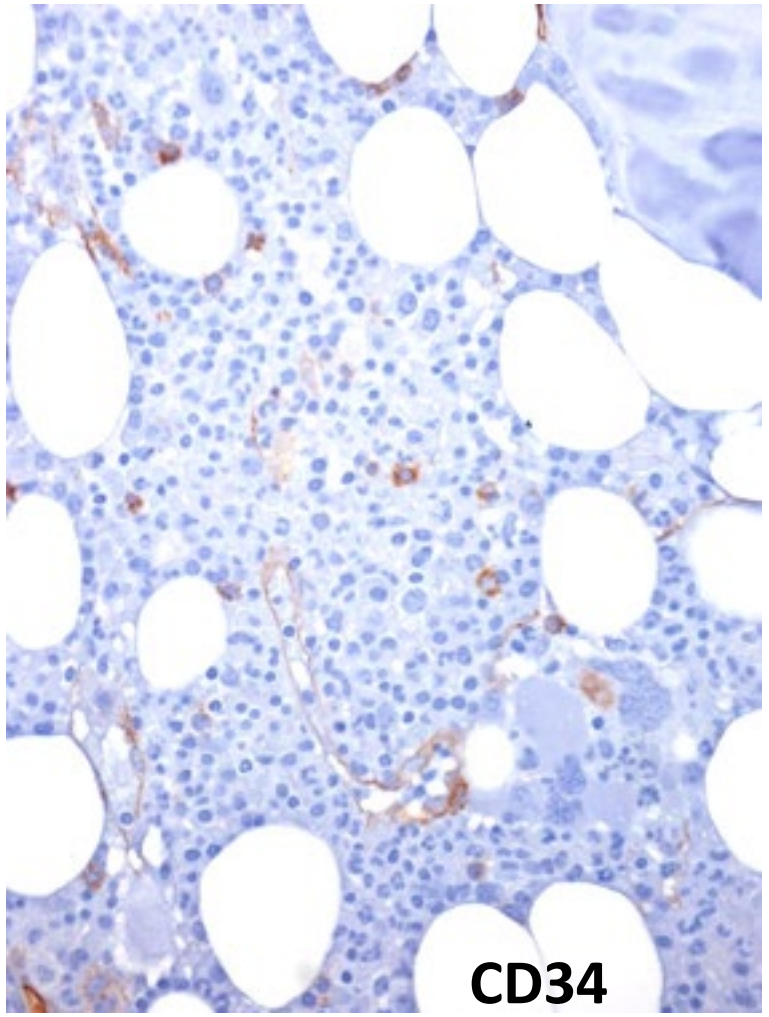


2012

- F, 58 y
- Thrombocytosis
- Hb and WBC within normal limit
- Spleen and liver within normal limit
- JAK2 V617F mutation: VAF 32%
- Cytogenetics: 46,XX






CD34

Evolving classifications

	WHO 2008	WHO 2017	WHO 2022	ICC 2022
2012	Ph- MPN, ET	Ph- MPN, ET	Ph- MPN, ET	Ph- MPN, ET

Therapy: HU, periodic follow up

September 2023

- 69 y
- Leukocytes 1.830 x10^9/L
- Hemoglobin 63 g/L
- Platelets 112 x10^9/L
- LDH 1021 mU/mL

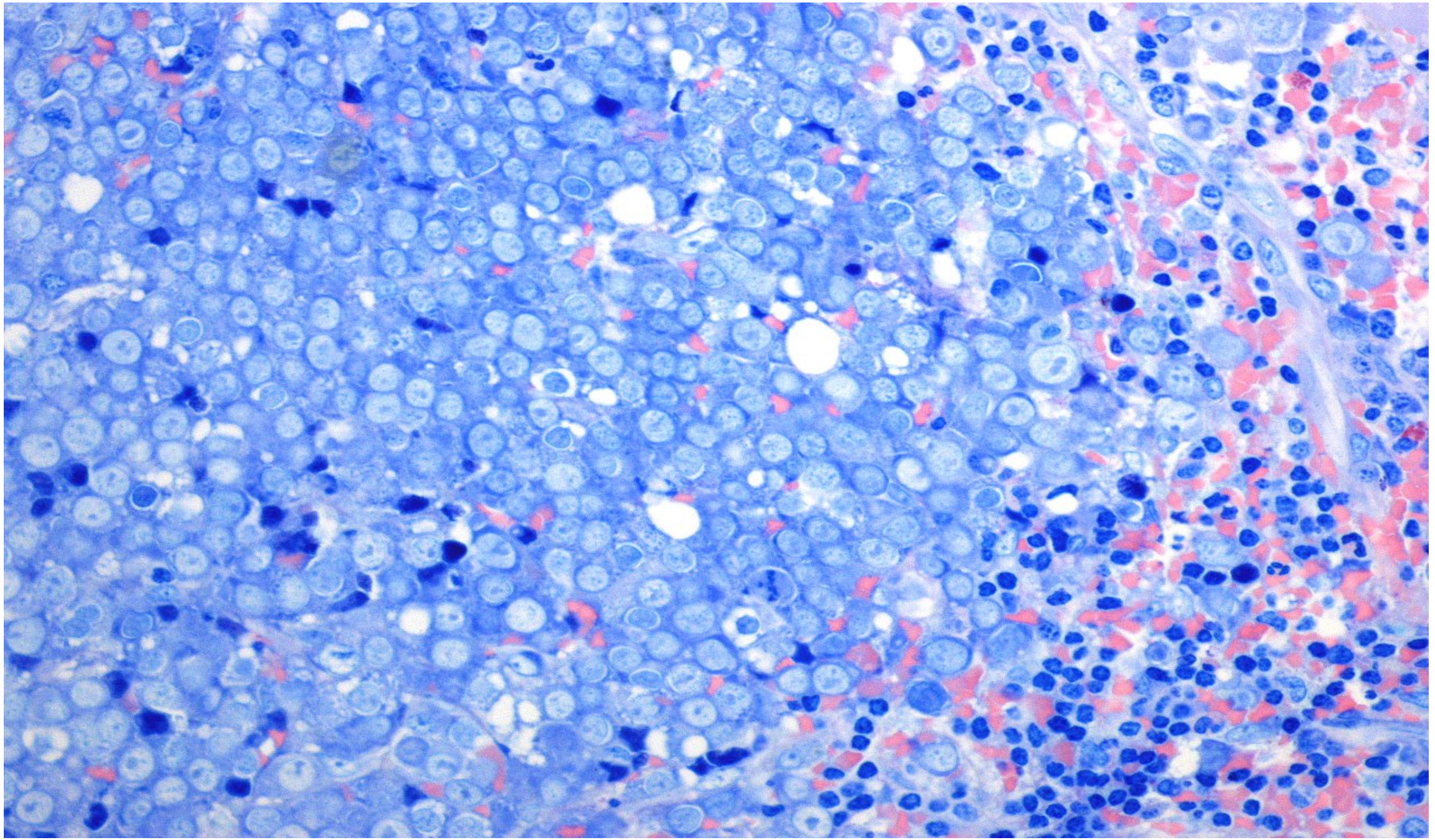
- Exclusion of iron, vitamin B12, folic acid deficiency
- Interruption of cytoreduction

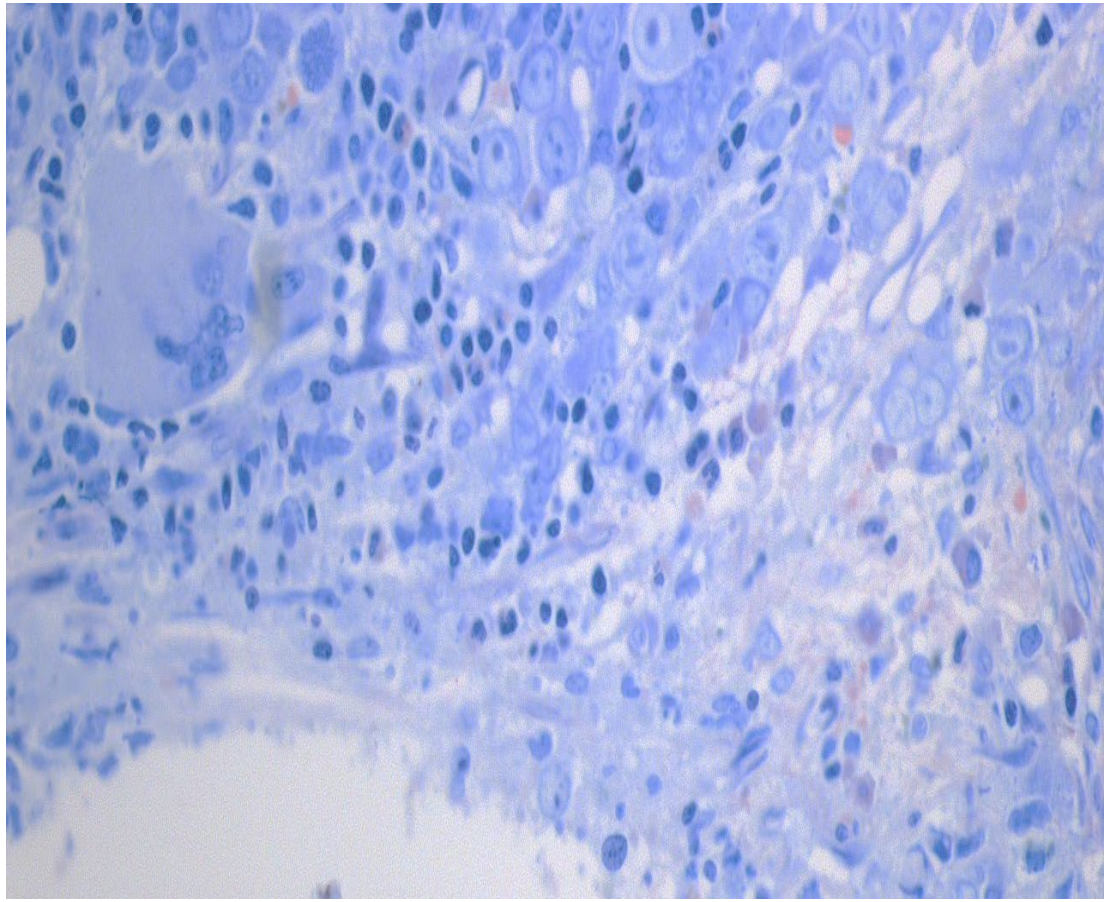
Persistence of pancytopenia

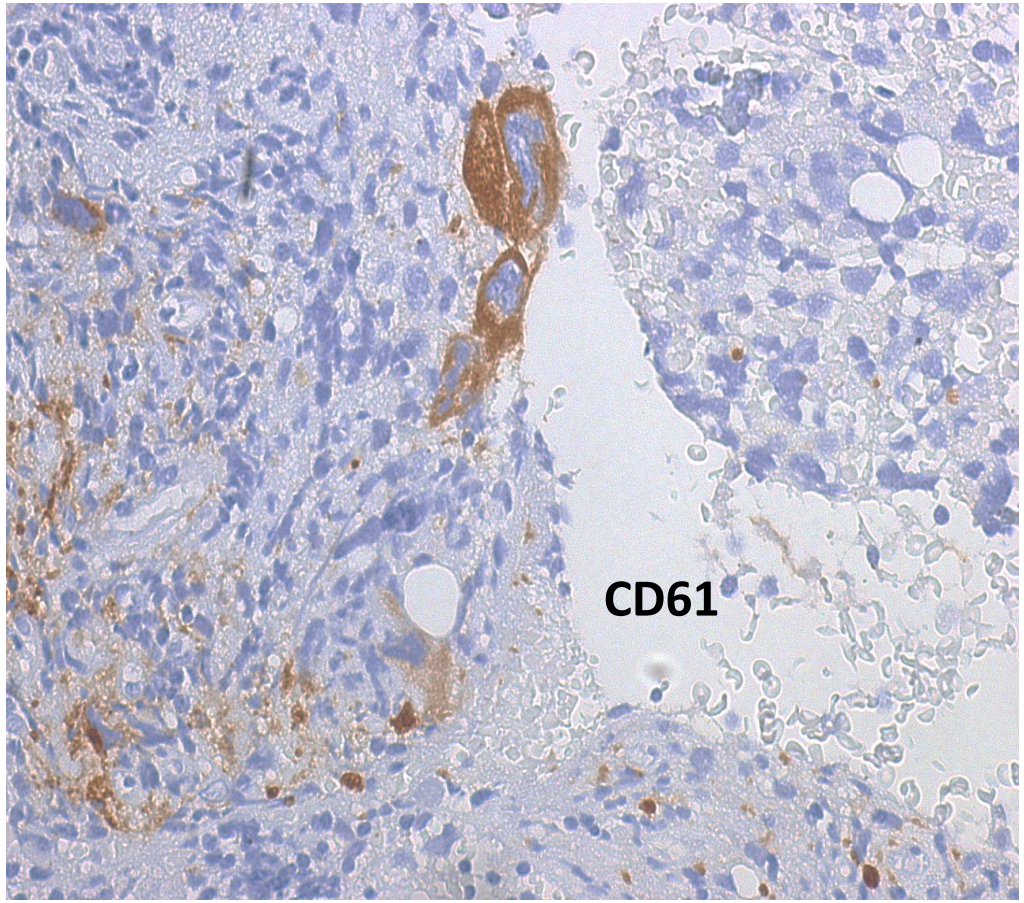
BM examination

BM re-evaluation in Ph- MPN

- Evolution towards:
  - Post-ET myelofibrosis
  - Acute leukemia
- Therapy-related modification(s)



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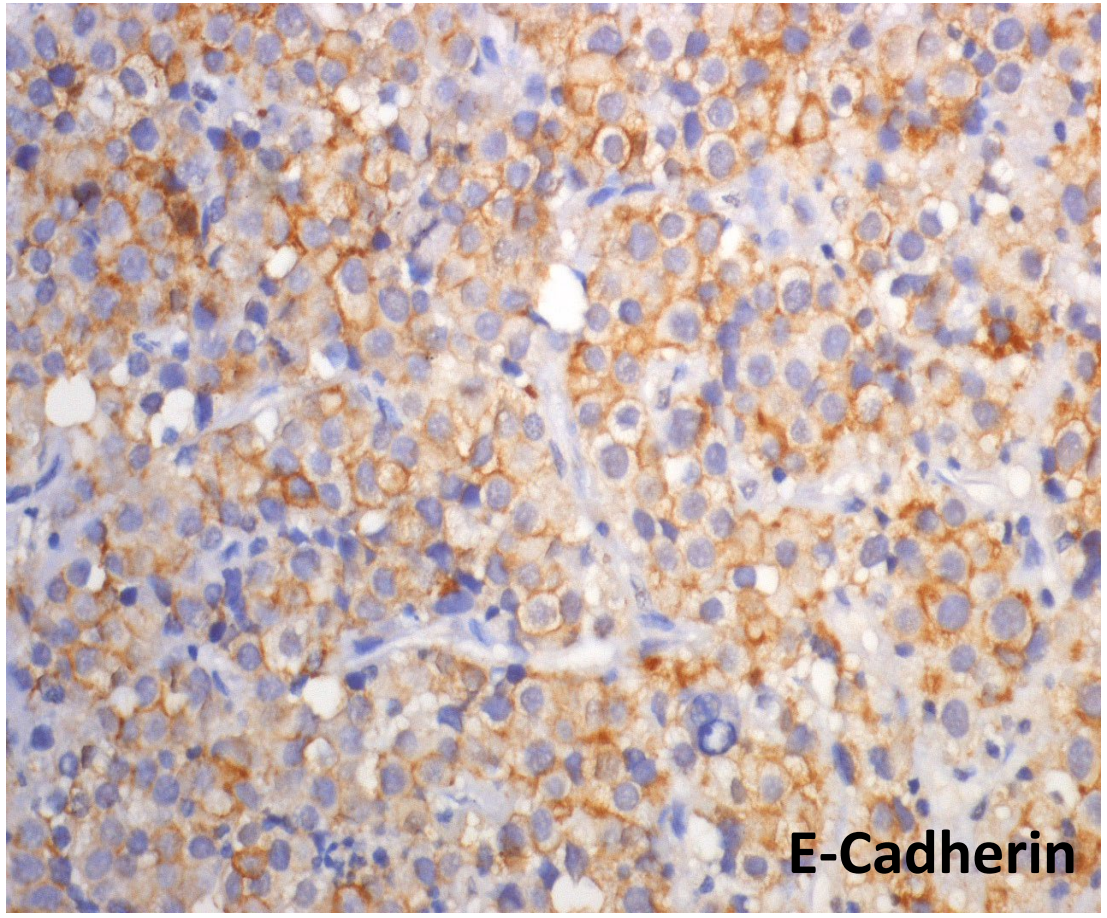
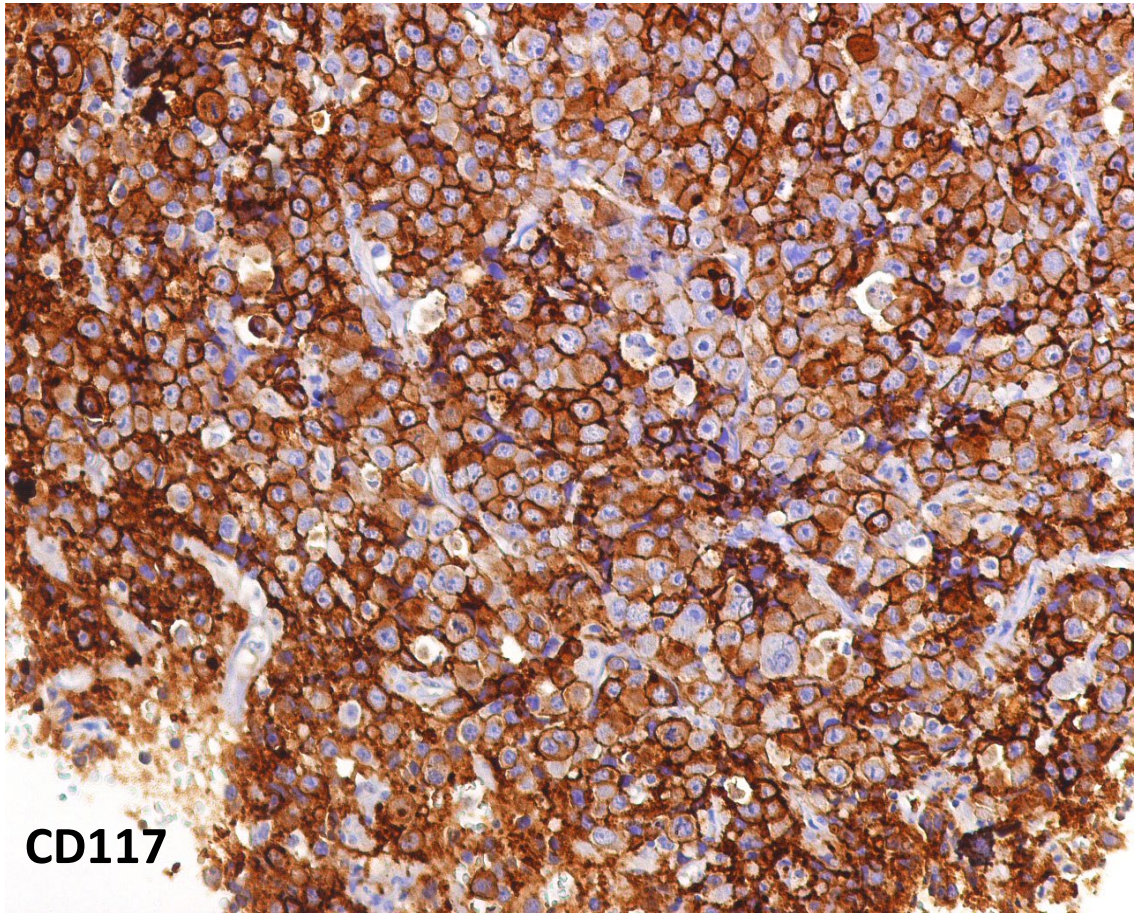

E-Cadherin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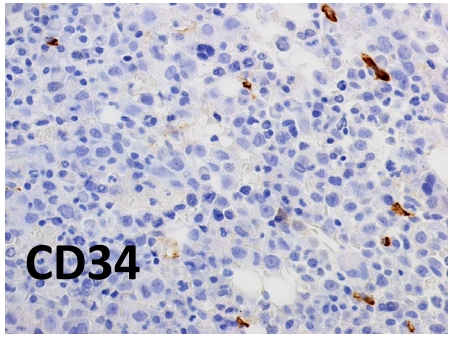
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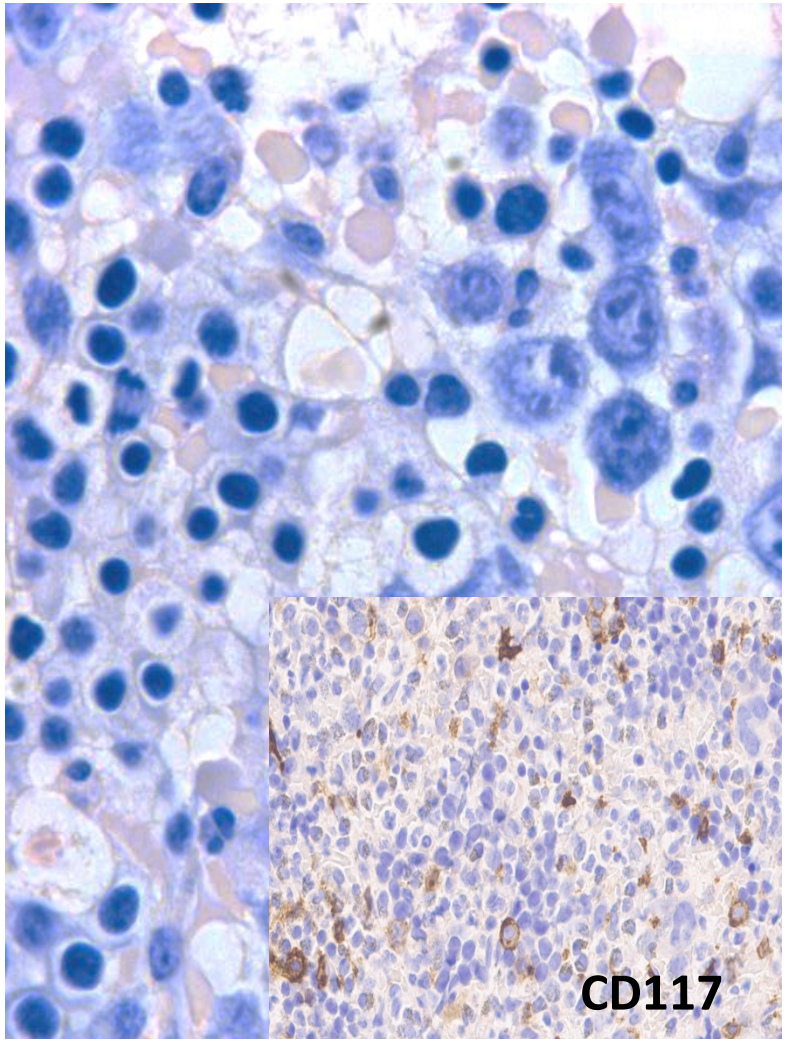
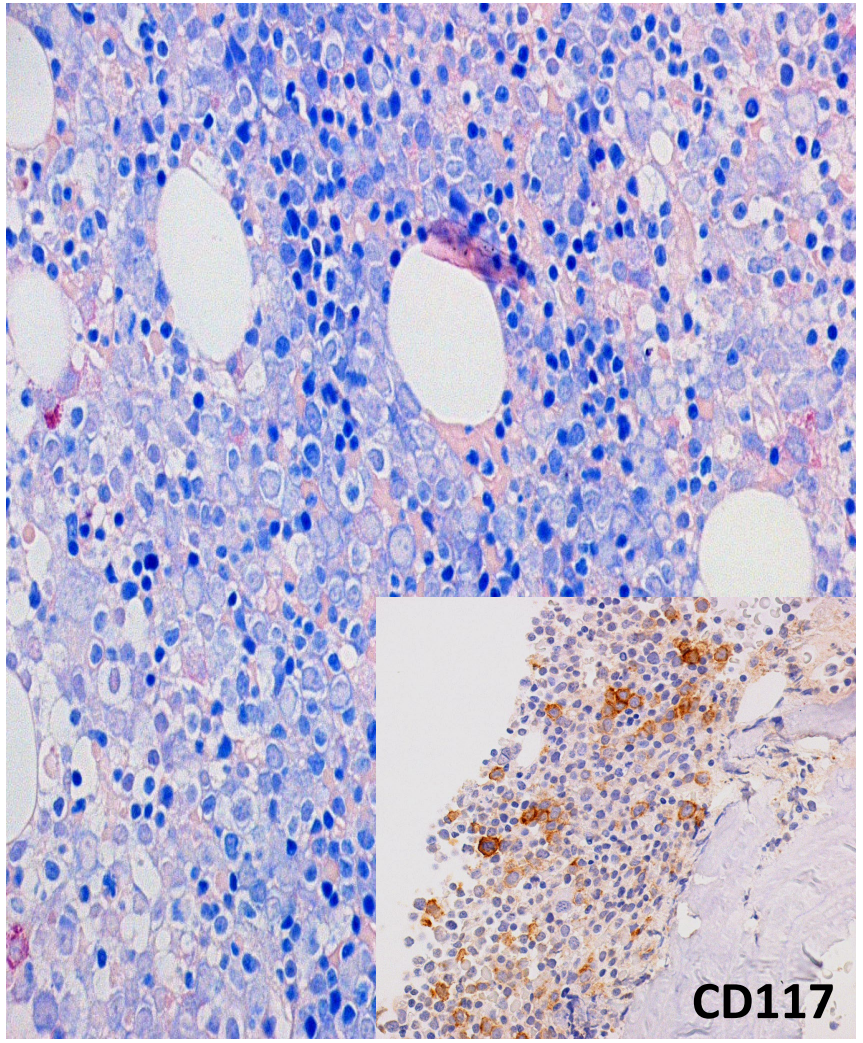
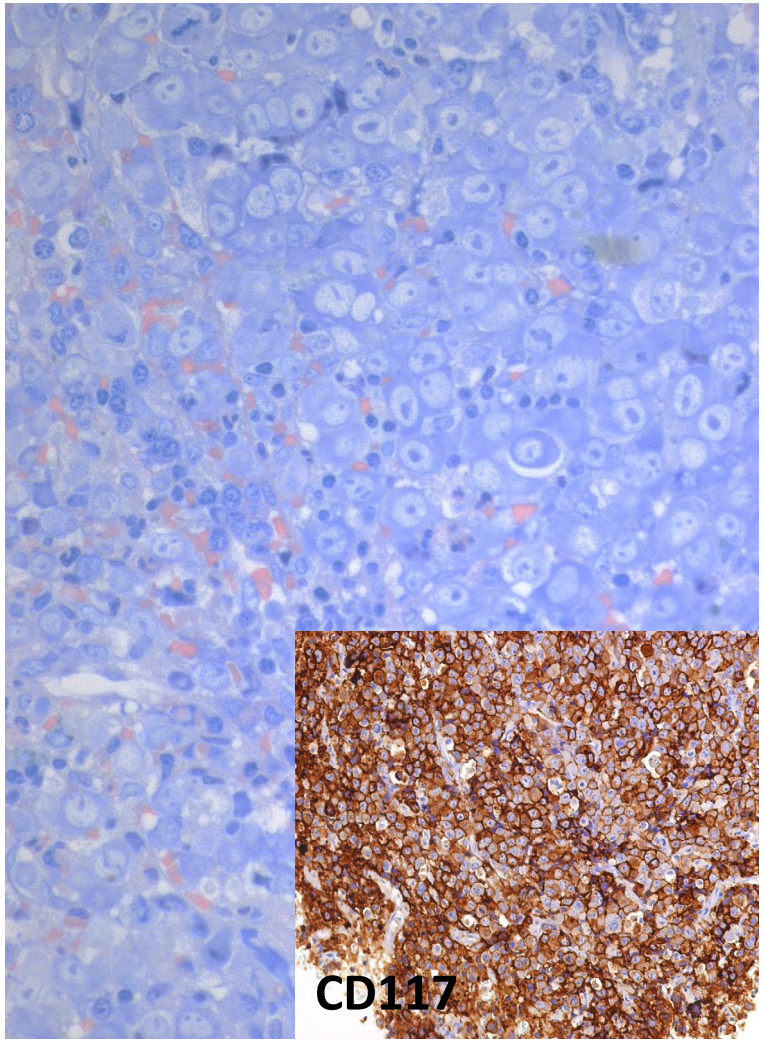
Megaloblastic changes



MDS-ery



Our case



WHO 2017

Table 1.01 Diagnostic approach to myeloid neoplasms in which erythroid precursors constitute ≥ 50% of the nucleated bone marrow (BM) cells

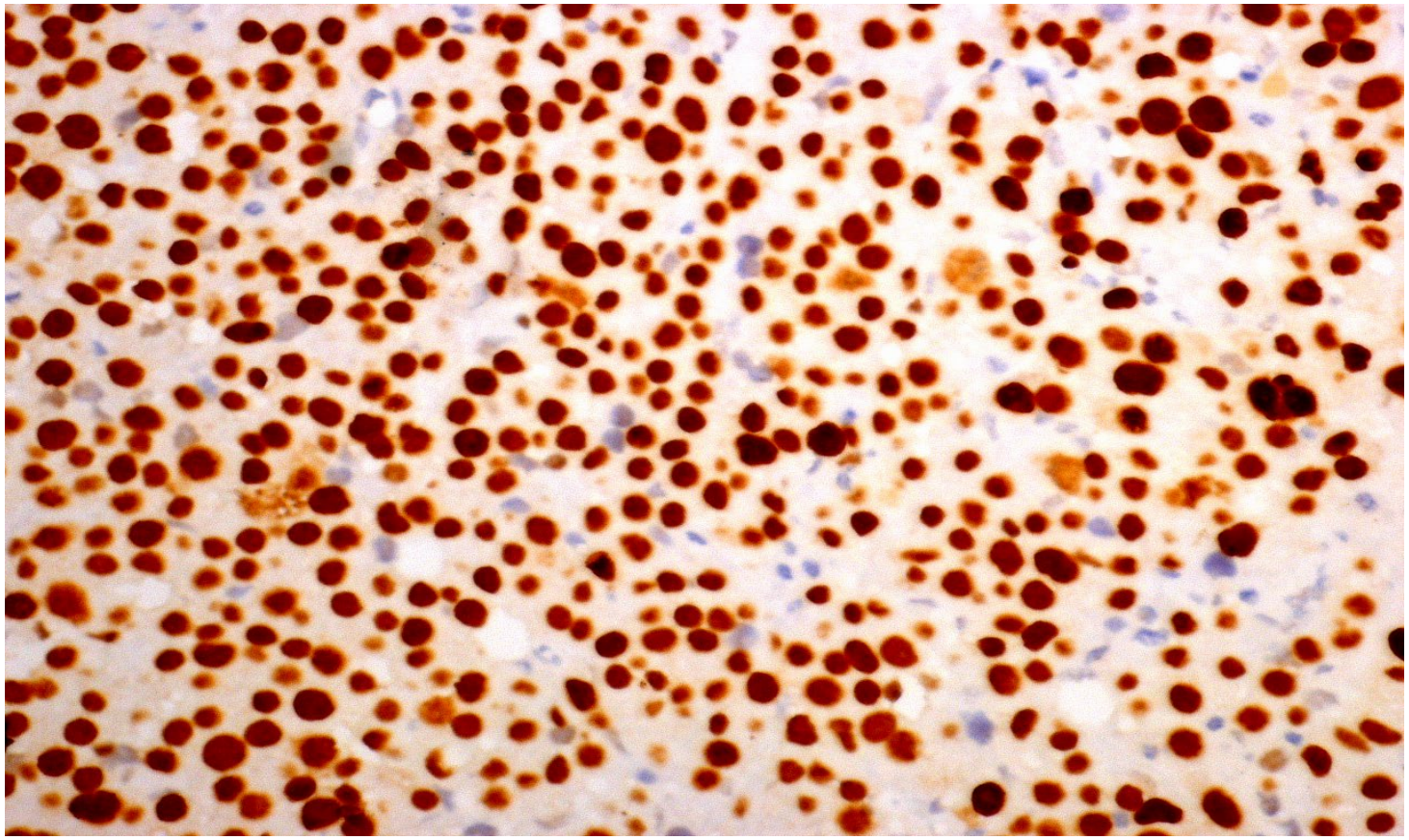
Percentage of BM cells that are erythroid precursors	Percentage of BM (or PB) cells that are myeloblasts	Prior therapy	Defining WHO genetic abnormality present	Meets criteria for AML with myelo-dysplasia-related changes	4th Edition diagnosis (2008)	Revised 4th edition diagnosis (2017)
≥ 50%	n/a	yes	n/a	n/a	Therapy-related myeloid neoplasm	Therapy-related myeloid neoplasm
≥ 50%	≥ 20%	no	yes	n/a	AML with recurrent genetic abnormality	AML with recurrent genetic abnormality
≥ 50%	≥ 20%	no	no	yes	AML with myelodysplasia-related changes	AML with myelodysplasia-related changes
≥ 50%	≥ 20%	no	no	no	AML, NOS; acute erythroid leukaemia (erythroid/myeloid subtype)	AML, NOS (a non-erythroid subtype)
≥ 50%	< 20%, but ≥ 20% of non-erythroid cells	no	no[a]	n/a	AML, NOS; acute erythroid leukaemia (erythroid/myeloid subtype)	MDS[b]
≥ 50%	< 20%, and < 20% of non-erythroid cells	no	no[a]	n/a	MDS[b]	MDS[b]
> 80% immature erythroid precursors with > 30% proerythroblasts	< 20%	no	no[a]	n/a	AML, NOS; acute erythroid leukaemia (pure erythroid subtype)	AML, NOS; pure erythroid leukaemia

AML, acute myeloid leukaemia; BM, bone marrow; MDS, myelodysplastic syndrome; n/a, not applicable; NOS, not otherwise specified; PB, peripheral blood.

[a] Cases of AML with t(8;21)(q22;q22.1) resulting in the *RUNX1-RUNX1T1* fusion protein, AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22) resulting in the *CBFB-MYH11* fusion protein, or acute promyelocytic leukaemia with the *PML-RARA* fusion protein may rarely occur in this setting with < 20% blasts, and those diagnoses take precedence over the diagnosis of either AML, NOS or MDS.

[b] Classify according to the myeloblast percentage of all BM cells and PB leukocytes, along with other MDS criteria.

Our case: p53 protein over-expression



Journal of Hematopathology (2021) 14:15–22
https://doi.org/10.1007/s12308-020-00431-7

ORIGINAL ARTICLE

p53 immunohistochemistry discriminates between pure erythroid leukemia and reactive erythroid hyperplasia

Christina Alexandres[1] · Basma Basha[2] · Rebecca L. King[3] · Matthew T. Howard[3] · Kaaren K. Reichard[3]

What about *TP53* gene?
And *JAK2*?

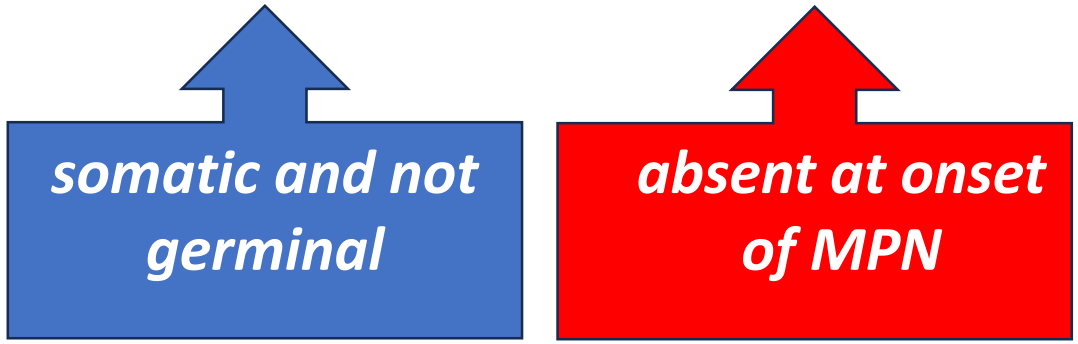
NGS analysis on BMMC at time of evolution (2023)

- *TP53:*
  - ❑R273H (missense): VAF 91.6%
  - ❑R282W (missense): VAF 1.2%
- *JAK2:*
  - ❑V617F (missense): VAF 71,6%

- ***Germinal?***
- ***Somatic?***
  - ***If somatic, present at time of ET diagnosis?***

The importance of being… far sighted
NGS on PBMC at diagnosis of ET (2012)

	2012 (PBMC, VAF)		2023 (BMMC, VAF)
	T-lymphocytes	Circulating NC	
JAK2 V617F	Absent	32%	71,6%
TP53 R273H	Absent	Absent	91.6%
TP53 R282W	Absent	Absent	1.2%



Cytogenetics: chromosome 17 deletion

Diagnosis

WHO 2022

- Acute erythroid leukemia

Table 7. Acute myeloid leukaemia.

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 2022

- Acute myeloid leukemia (AML) with mutated TP53

…moving to a more genetically-defined classification

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* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
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%)

Our patient: supportive care, DOD within weeks from diagnosis

A History and Current Understanding of Acute Erythroid Leukemia

Coltoff Alexander

Clinical Lymphoma, Myeloma and Leukemia, Vol. 23, No. 8, 583–588 © 2023

- Giovanni Di Guglielmo is credited for the first description of an erythroid-predominant leukemia in the early 20th century
- Pancytopenia is the most frequent clinical presentation

Table 1 Evolution of Diagnostic Criteria and Nomenclature of Erythroid-predominant Myeloid Neoplasms

Year	Criteria	Nomenclature	Definition
1976	FAB [a] Co-operative group	AML-M6	1. Erythroid precursors ≥ 30% 2. Dyserythropoiesis ≥ 10%
1985	Revised FAB Co-operative group	AML-M6	1. Erythroblasts ≥ 50% of all nucleated bone marrow cells 2. Prominent dyserythropoiesis 3. Myeloblasts ≥ 30% of the nonerythroid cell population
2001	WHO[b] 3rd Edition	Acute erythroid/myeloid leukemia Pure erythroid leukemia	1. Erythroid precursors ≥ 50% of all bone marrow cells 2. Myeloblasts ≥ 20% of the nonerythroid cell population 1. Erythroid precursors with minimal differentiation ≥ 80% of all marrow cells 2. No significant myeloblastic component
2008	WHO 4th Edition	Erythroleukemia, erythroid/myeloid Pure erythroid leukemia	1. Erythroid precursors ≥ 50% of all bone marrow cells 2. Myeloblasts ≥ 20% of the nonerythroid cell population 1. Erythroid precursors with minimal differentiation ≥ 80% of all marrow cells 2. No significant myeloblastic component
2016	Revised WHO 4th Edition	Acute erythroid leukemia (pure erythroid type)	1. Erythroid precursors > 80% of all bone marrow cells of which ≥ 30% proerythroblasts
2022	WHO 5th Edition	Acute erythroid leukemia	1. Erythroid precursors > 80% of all bone marrow cells of which ≥ 30% proerythroblasts (cases with erythroid precursors < 80% of cellularity are recognized)
2022	International Consensus Classification of Myeloid Neoplasms	AML with mutated TP53	1. ≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia 2. Any somatic TP53 mutation (VAF > 10%)

Received: 3 February 2023 | Revised: 28 February 2023 | Accepted: 2 March 2023

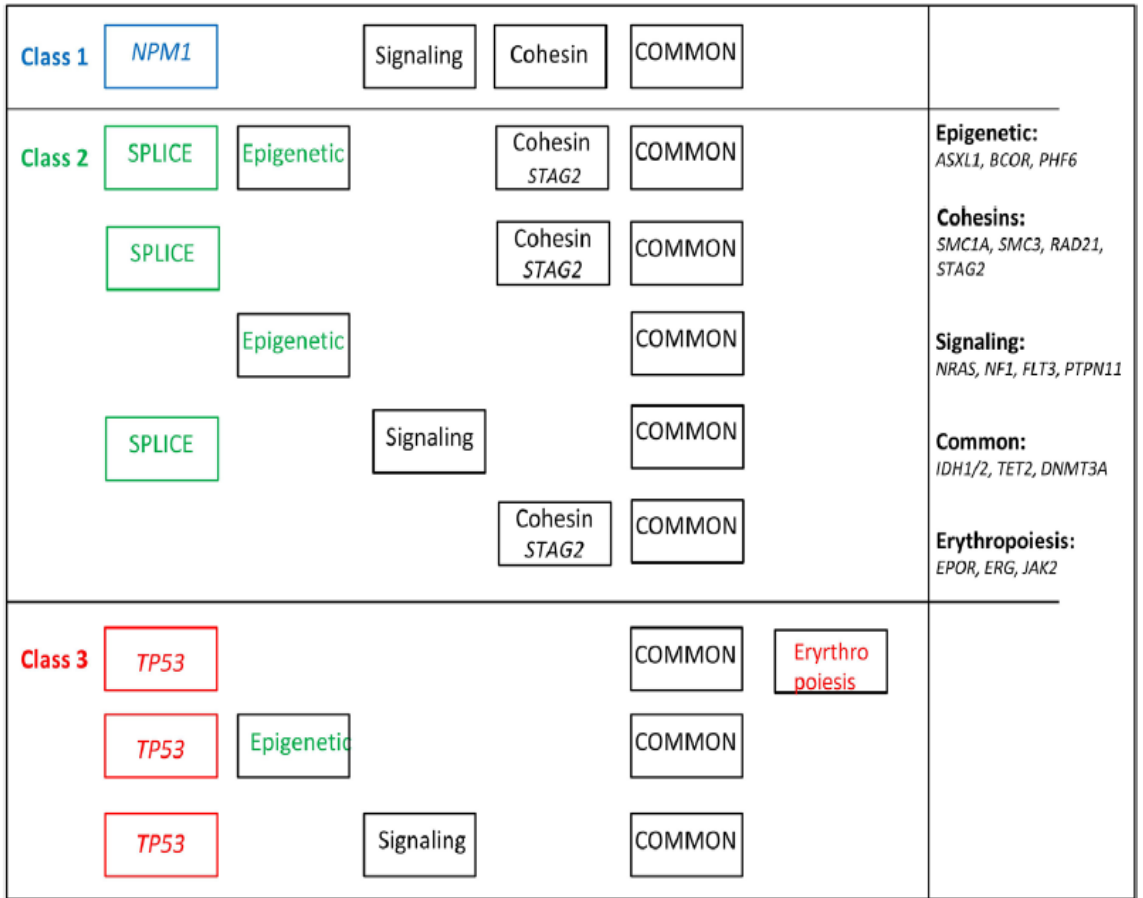
DOI: 10.1002/jha2.676

eJHaem

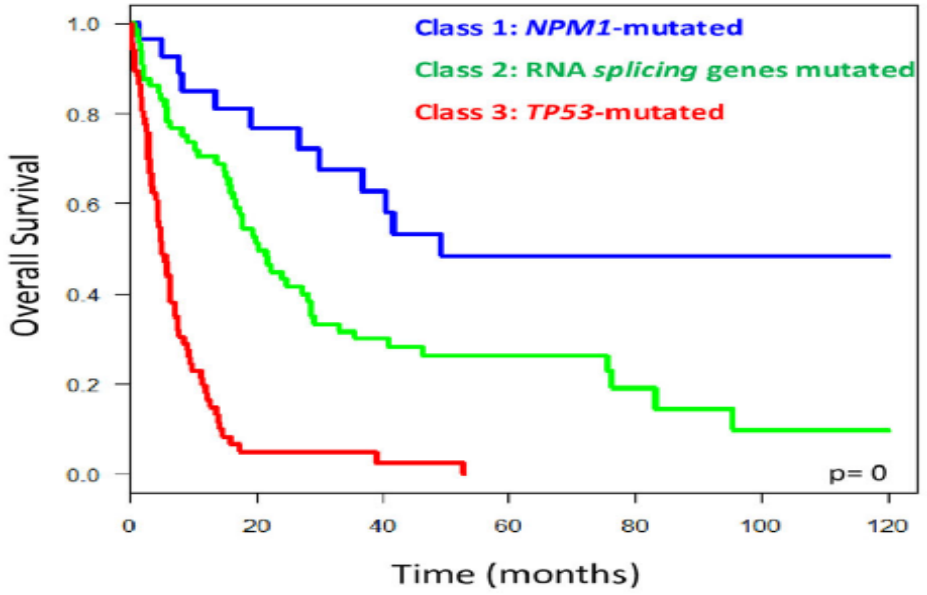
SHORT REPORT

Erythroleukemia: Classification

Nathalie Cervera[1] | Arnaud Guille[1] | José Adélaïde[1] | Marie-Anne Hospital[2] | Sylvain Garciaz[2] | Marie-Joelle Mozziconacci[3] | Norbert Vey[2] | Véronique Gelsi-Boyer[1,3] | Daniel Birnbaum[1]



- As in other AMLs, additional alterations can be seen, especially in the *TP53*-mutated class 3 (partial / complete losses of 5q, 7q, 17p, 20q, deletions / breaks of *ETV6* at 12p, complex karyotypes).
- Pure AELs can harbor more than one *TP53* alteration
- Class 3 AELs may be secondary too, including to treatment for a previous disease



	Cases	events	median of survival		
Class 1: *NPM1*-mutated	27	12	49.3	p= 4e-04	p= 0.02
Class 2: RNA *splicing* genes mutated	64	50	20.2		
Class 3: *TP53*-mutated	66	64	5.0	p= 0.61	

Blood Cancer Journal www.nature.com/bcj

Blood Cancer Journal (2022)12:147

ARTICLE OPEN

Check for updates

Pure (acute) erythroid leukemia: morphology, immunophenotype, cytogenetics, mutations, treatment details, and survival data among 41 Mayo Clinic cases

Kaaren K. Reichard[1], Ayalew Tefferi[2], Maymona Abdelmagid[2], Attilio Orazi[3], Christina Alexandres[4], Joanna Haack[1] and Patricia T. Greipp[1]

- Five pts: disease progression from an underlying MPN (2 PV, 2 ET, 1 PMF) with NGS evidence of *JAK2* V617F mutation.
- All 41 cases showed double *TP53* alterations
  - ❑ two *TP53* deletions by karyotype (3%; N = 1),
  - ❑ double *TP53* mutations by NGS (29%; N = 12)
  - ❑ a combination of a *TP53* deletion and *TP53* mutation (68%; N = 28).

Primary : 14 cases
Therapy-related: 14 cases
Secondary: 12 cases
Undetermined: 1 case

Our case: secondary? Therapy-related?

Clonal architecture evolution in Myeloproliferative Neoplasms: from a driver mutation to a complex heterogeneous mutational and phenotypic landscape

Leukemia (2023) 37:957–963;

Nabih Maslah[1,2], Lina Benajiba[3,4], Stephane Giraudier[1,2], Jean-Jacques Kiladjian[2,4,5]✉ and Bruno Cassinat[1,2,5]

- Driver mutations (JAK2, CALR, MPL) but also additional mutations
  - intracellular signaling pathways, epigenetics (DNA methylation, post-translational modifications of histones), transcription factors, RNA splicing
- Both driver and additional mutations can be the first clonal event
- Intra-tumor heterogeneity (ITH) = molecularly and phenotypically distinct subclones
- Acquisition of several mutations over long periods, with certain mutations having an impact on the clinical course
  - *ASXL1, EZH2, SRSF2* and *IDH1/2* mutation = high molecular risk (HMR) in PMF pts
  - *TP53, N/K-RAS, NFE2* associated with poorer outcome
  - *TP53* mutations associated with risk of leukemic evolution in ET
- Accumulation of mutations is in itself an adverse prognostic factor in MPNs
  - Definition of prognostic scores including molecular data (MIPSS70, MIPSS70+, MTSS)
- Treatments during the long chronic phase can actively shape clonal fitness and evolution

Low-burden *TP53* mutations in chronic phase of myeloproliferative neoplasms: association with age, hydroxyurea administration, disease type and *JAK2* mutational status

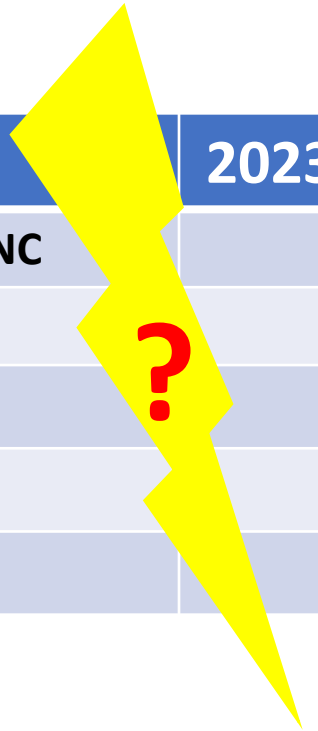
Leukemia (2018) **32**, 450–461

B Kubesova[1,6], S Pavlova[1,2,6], J Malcikova[1,2], J Kabathova[1], L Radova[2], N Tom[2], B Tichy[2], K Plevova[1,2], B Kantorova[1,2], K Fiedorova[2], M Slavikova[2], V Bystry[2], J Kissova[3], B Gisslinger[4], H Gisslinger[4], M Penka[3], J Mayer[1,2], R Kralovics[5], S Pospisilova[1,2] and M Doubek[1,2]

- In chronic MPN phase, *TP53* defects are extremely rarely detected by Sanger sequencing or cytogenetics
- BUT they were shown to be common in post-MPN AML
- *TP53* mutations can be traced months or even years before leukemic transformation
  - Mutational burden remain low until complete p53 inactivation by losing the second allele (17p defects or second mutation), followed by rapid clonal expansion
- Different sensibility of detection methods of *TP53* alterations
  - Cytogenetics < Sanger seq < RT-PCR < “standard” NGS < “high sensibility” NGS
- Using ultra-deep NGS
  - *TP53* mutations are strongly associated with age in MPN
  - No significant age-independent association with HU therapy, disease type or MPN driver gene mutations

In our case

	2012 (PBMC, VAF)		2023 (BMMC, VAF)
	T-lymphocytes	Circulating NC	
JAK2 V617F	Absent	32%	71,6%
TP53 R273H	Absent	Absent	91.6%
TP53 R282W	Absent	Absent	1.2%
Karyotype	46, XX		del chr 17



When did TP53 alterations develop?
How fast did TP53 alterations lead from chronic MPN to AML?

Blood Cancer Journal www.nature.com/bcj

Blood Cancer Journal (2022)12:147

ARTICLE OPEN

Check for updates

Pure (acute) erythroid leukemia: morphology, immunophenotype, cytogenetics, mutations, treatment details, and survival data among 41 Mayo Clinic cases

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… pathologists may experience trepidation in rendering such a diagnosis given the gravity of a reported approximately <6 month overall median survival

Multidisciplinary approach:

- **Hematologists**
- **Pathologists**
- **Biologists and Technicians (FC, cytogenetics and molecular analyses)**

Thanks:

Prof Elisa Rumi, Dr Oscar Borsani, Dr Cristina Picone, Dr Daniela Pietra

SC Ematologia

Dr Erica Travaglino, Dr Francesca Antoci

SC Anatomia Patologica