FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinica e Terapia delle Sindromi Mielodisplastiche

28 maggio 2022

Classificazione WHO e diagnosi morfologica delle MDS

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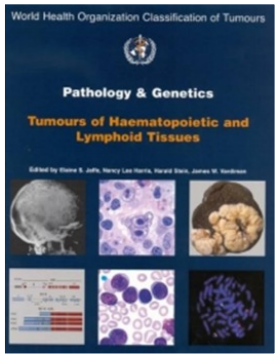
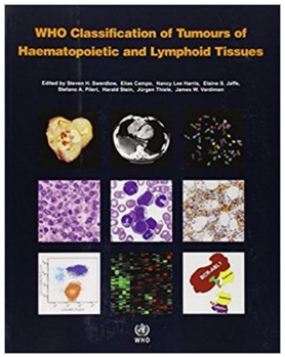
Gemelli

The role of Morphology

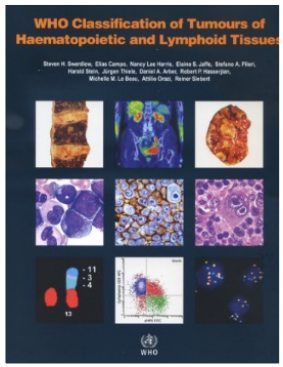
WHO diagnostic guidelines are to date worldwide adopted:
in the appropriate setting
Morphology is a diagnostic tool
which should be integrated with flow-cytometry,
cytogenetics/molecular genetics, histology and clinical presentation.



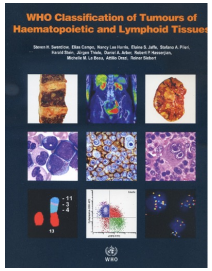
WHO 1999: pages 351



WHO 2008: pages 439



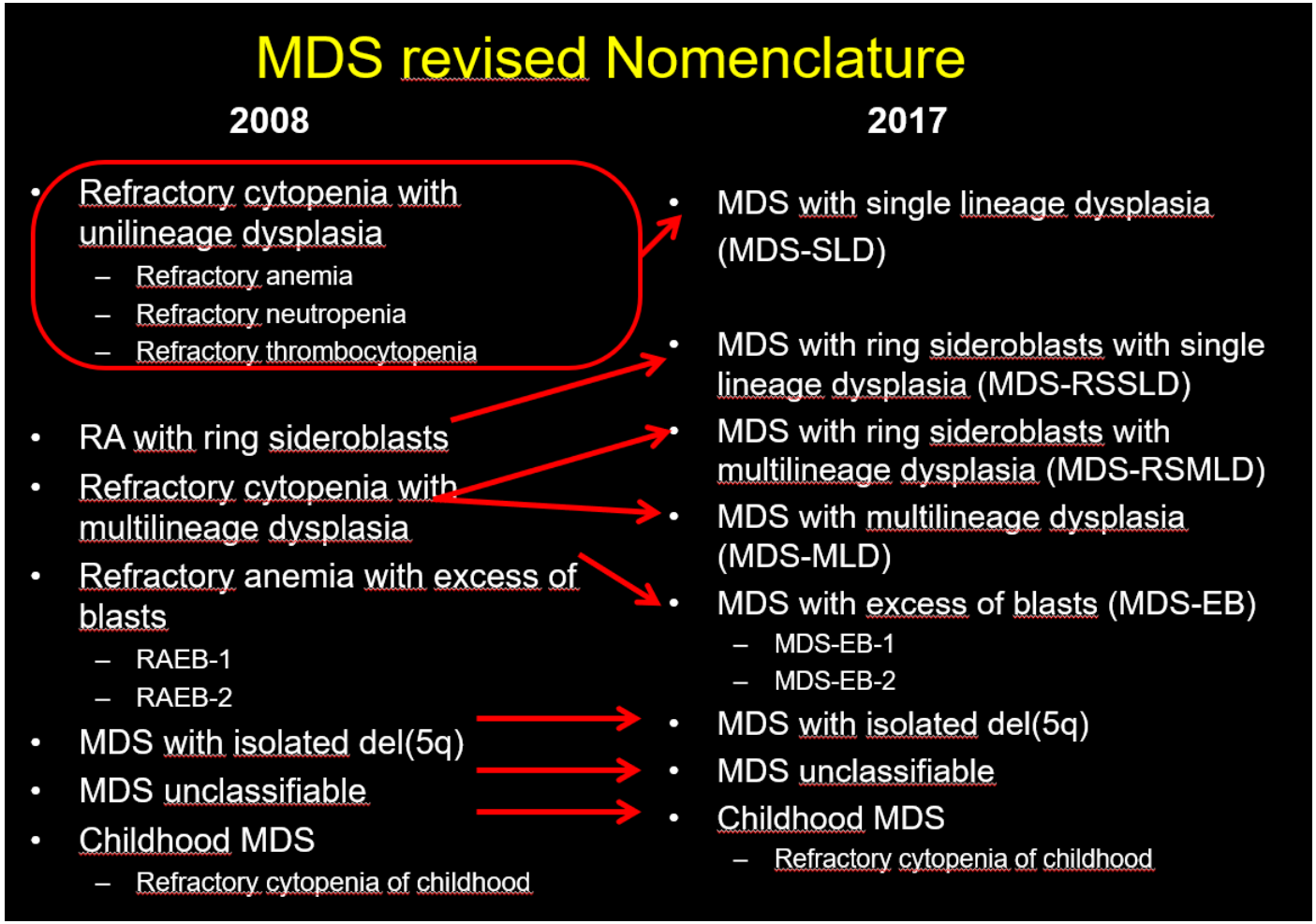
WHO 2017: pages 585

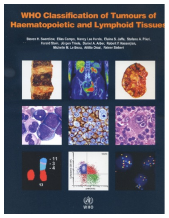


WHO 2017: Proposed changes (I)

➢ Nomenclature

- WHO classifies based on dysplasia and blast count, not cytopenia
- Type of dysplasia often does not fit with the cytopenic lineage in RCUD
- Subgroups of RA,RN and RT are eliminated

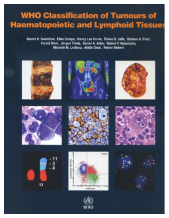




WHO 2017: Proposed changes (II)

MDS Morphology Issues

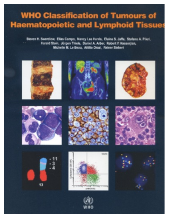
- Cut-off of 10% to detect lineage dysplasia is maintained
- Cut-off of 2% of blasts introduced by the IPSS-R:
  - difficult, poorly reproducible distinction between categories
    0-2% vs >2% vs <5%
  - Recommendation to report the exact blast count, rather than <5%
- Diagnosis of AML in cases with less than 20% of blasts
  - detection of t(8;21)(q22;q22); *RUNX1-RUNX1T1*; inv(16)(p13.1;q22) *or* (16;16)(p13.1;q22); *CBFB-MYH11* or *PML-RARA* is still considered diagnostic for AML regardless of blast count
  - detection of other genetics event such as t(9;11)(p21.3;q23.3); *KMT2A-MLLT3*, t(6;9)(p23;q34.1), *DEK-NUP214* and *NPM1* mutation remain controversial
- Similarities between myeloid neoplasms with inv3(q21;q26.2) or t(3;3)(q21.3;q26.2) regardless of blast count



WHO 2017: Proposed changes (III)

MDS Unclassifiable

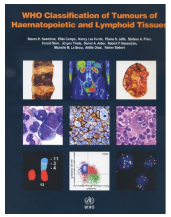
- MDS with single lineage dysplasia or multilineage dysplasia with <5% of blasts in the BM but 1% of blasts in PB:
  - Recommendation: 1% of blasts in PB must be measured on at least two separate occasions
- MDS with single lineage dysplasia but pancytopenia:
  - Recommendation: cytopenia is below IPSS level: ANC <1.8x10^9/L, HGB<10g/dL, PLT<100x10^9/L
- MDS-associated cytogenetic abnormality in association with cytopenias, <1% PB and <10% BM blasts, but <10% dysplasia in any cell line



WHO 2017: Proposed changes (IV)

Immunophenotyping in MDS

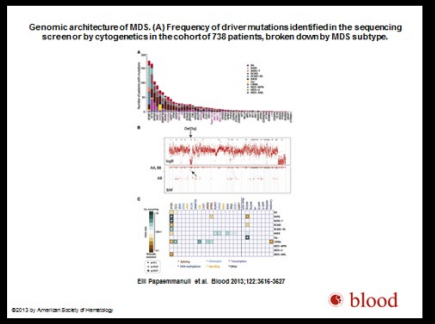
- Abnormal flow cytometry patterns do predict MDS with good sensitivity and specificity
- Specific antibody panels should be carefully chosen and validated according to published guidelines
- Flow cytometry results should be integrated with the BM morphology report
- Flow cytometry immunophenotyping:
  - ➢ Is not required but will be considered as “supportive” of MDS
  - ➢ Will not alone be sufficient for making diagnosis of MDS

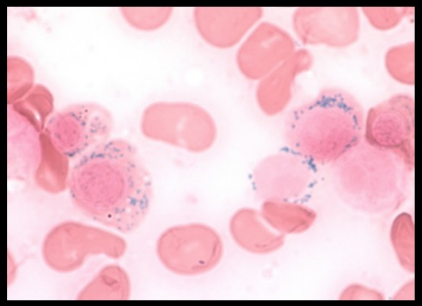


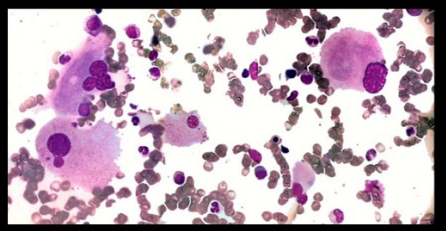
WHO 2017: Proposed changes (V)

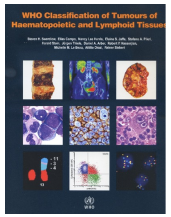
Genetics in MDS

- ✓ Somatic mutations in MDS
  - Prognostic significance of mutations of *TP53, EZH2, ETV6, RUNX1, ASXL1* and others.
- ✓ Mutation of the spliceosoma gene *SF3B1* in MDS with ring sideroblasts (MDS-RSSLD & MDS-RSMLD)
  - ≥15% ring sideroblasts (among erythroid precursors) *or*
  - ≥5% ring sideroblasts in presence of an *SF3B1* mutation
  - Blasts cell increase exclude this diagnosis
  - If multilineage dysplasia without a blast cell increase is present, a case is classified as MDS with ring sideroblasts and multilineage dysplasia.
- ✓ MDS with isolated del(5q)
  - Del(5q) as the only abnormality
  - Except for monosomy 7, WHO 2016 does not allow a second cytogenetic abnormality for this category
  - Recommendation to assess *TP53* mutation or p53 staining.



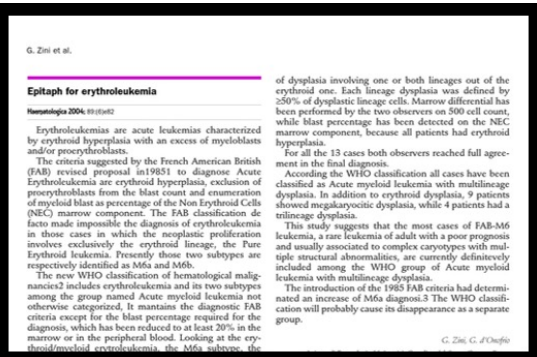






WHO 2017: Proposed changes (VI)

Acute erythroid leukemia (erythroid/myeloid type)* proposed to become MDS with excess of blasts



G. Zini et al.

Epitaph for erythroleukemia

Haematologica 2004; 89:(6):e82

Erythroleukemias are acute leukemias characterized by erythroid hyperplasia with an excess of myeloblasts and/or proerythroblasts.

The criteria suggested by the French American British (FAB) revised proposal in1985[1] to diagnose Acute Erythroleukemia are erythroid hyperplasia, exclusion of proerythroblasts from the blast count and enumeration of myeloid blast as percentage of the Non Erythroid Cells (NEC) marrow component. The FAB classification de facto made impossible the diagnosis of erythroleukemia in those cases in which the neoplastic proliferation involves exclusively the erythroid lineage, the Pure Erythroid leukemia. Presently those two subtypes are respectively identified as M6a and M6b.

The new WHO classification of hematological malignancies2 includes erythroleukemia and its two subtypes among the group named Acute myeloid leukemia not otherwise categorized, It mantains the diagnostic FAB criteria except for the blast percentage required for the diagnosis, which has been reduced to at least 20% in the marrow or in the peripheral blood. Looking at the erythroid/myeloid erythroleukemia, the M6a subtype, the of dysplasia involving one or both lineages out of the erythroid one. Each lineage dysplasia was defined by ≥50% of dysplastic lineage cells. Marrow differential has been performed by the two observers on 500 cell count, while blast percentage has been detected on the NEC marrow component, because all patients had erythroid hyperplasia.

For all the 13 cases both observers reached full agreement in the final diagnosis.

According the WHO classification all cases have been classified as Acute myeloid leukemia with multilineage dysplasia. In addition to erythroid dysplasia, 9 patients showed megakaryocitic dysplasia, while 4 patients had a trilineage dysplasia.

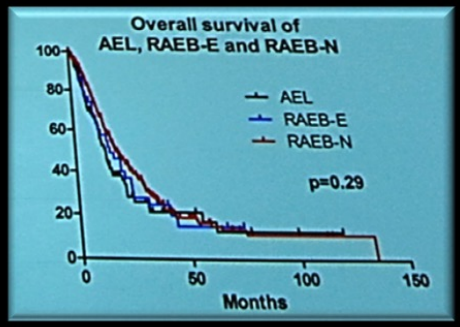
This study suggests that the most cases of FAB-M6 leukemia, a rare leukemia of adult with a poor prognosis and usually associated to complex caryotypes with multiple structural abnormalities, are currently definitevely included among the WHO group of Acute myeloid leukemia with multilineage dysplasia.

The introduction of the 1985 FAB criteria had determinated an increase of M6a diagnosi.3 The WHO classification will probably cause its disappearance as a separate group.

G. Zini, G. d'Onofrio

WHO 2001 & 2008 diagnostic criteria:

- AML NOS ≥50% BM erythroid precursors & ≥20% blasts NEC



WHO 2017

- These cases will now be classified as MDS based on the blasts ANC count.

the different AML and myelodysplastic syndrome (MDS) subtypes with predominant erythropoiesis may be combined into one category

*Pure erythroid leukemia remains a subtype of AML

Blurred borders of MDS & four-letters words

Table 1. Acronyms describing clonal hematopoiesis and related conditions

Acronym	*Condition*	*Description/Definition*
ARCH	Aging related clonal hematopoiesis	Describes the presence of detectable, benign clonal hematopoiesis (defined by the presence of somatic mutations in the blood or bone marrow) whose incidence increases with age. No formal definition involving clonal abundance or types of mutations. No clinical significance is implied.
CHIP	Clonal hematopoiesis of indeterminate potential	Defined by somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at ⩾ 2% variant allele frequency in individuals without a diagnosed hematologic disorder.
CHOP	Clonal hematopoiesis of oncogenic potential	Describes clonal hematopoiesis in a clinical context where it is associated with a significant likelihood of progressing to a frank malignancy.
IDUS	Idiopathic dysplasia of undetermined significance	Individuals with unexplained morphologic dysplasia of blood cells who are not cytopenic. Can occur with or without clonal hematopoiesis.
ICUS	Idiopathic cytopenia of undetermined significance	Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder. Can occur with or without clonal hematopoiesis although often used to refer to cytopenias without evidence of clonal hematopoiesis.
CCUS	Clonal cytopenia of undetermined significance	Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder, but who have somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at ⩾ 2% variant allele frequency. Can be considered as the intersection between CHIP and ICUS.

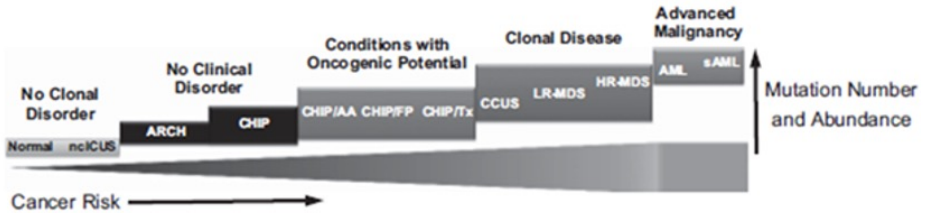


Figure 1. Variation of risk associated with clonal hematopoiesis in different clinical contexts. nclCUS, non-clonal idiopa undetermined significance; ARCH, aging related clonal hematopoiesis; CHIP, clonal hematopoiesis of indeterminate potent in the context of aplastic anemia; CHIP/FP, CHIP in the context of familial predisposition to MDS or AML; CHIP/Tx, CHIP myelotoxic therapy; CCUS, clonal cytopenia of undetermined significance; LR-MDS, lower risk myelodysplastic syndromes; H myelodysplastic syndromes; AML, acute myeloid leukemia; sAML, secondary acute myeloid leukemia.

R Bejar, 2017

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Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 × 10^9/L; and absolute neutrophil count, <1.8 × 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 × 10^9/L.

†If *SF3B1* mutation is present.

‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Dyserythropoiesis
- Nuclear
  - Nuclear budding
  - Internuclear bridging
  - Karyorrhexis
  - Multinuclearity
  - Nuclear hyperlobation
  - Megaloblastic changes
- Cytoplasmic
  - Ring sideroblasts
  - Vacuolization
  - Periodic acid-Schiff positivity

Dysgranulopoiesis
- Small or unusually large size
- Nuclear hypolobation (pseudo Pelger-Huët; pelgeroid)
- Irregular hypersegmentation
- Decreased granules; agranularity
- Pseudo Chediak-Higashi granules
- Auer rods

Dysmegakaryocytopoiesis
- Micromegakaryocytes
- Nuclear hypolobation
- Multinucleation (normal megakaryocytes are uninucleate with lobulated nuclei)

Diagnostic approach to myeloid neoplasms when erythroid precursors comprise ≥ 50% of BM nucleated cells

BM erythroid precursors	Myeloblast % of all cells in BM (or PB)	Prior therapy?	Recurring WHO genetic abnormality?	Meets criteria for AML-MRC?	Fourth edition diagnosis	Updated fourth edition diagnosis
≥50%	NA	Yes	NA	NA	Therapy-related myeloid neoplasm	Therapy-related myeloid neoplasm
≥50%	≥20%	No	Yes	NA	AML with recurring genetic abnormality	AML with recurring 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 leukemia (erythroid/ myeloid type)	AML, NOS (non erythroid subtype)
≥50%	<20%, but ≥20% of nonerythroid cells	No	No*	NA	AML, NOS, acute erythroid leukemia (erythroid/ myeloid subtype)	MDS†
≥50%	<20%, and <20% of nonerythroid cells	No	No*	NA	MDS†	MDS†
>80% immature erythroid precursors with ≥30% proerythroblasts	<20%	No	No*	NA	AML, NOS, acute erythroid leukemia (pure erythroid type)	AML, NOS, acute erythroid leukemia (pure erythroid type)

AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; NA, not applicable.

*Cases of AML t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*, AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11* or APL with *PML-RARA*, may rarely occur in this setting with <20% blasts and those diagnoses would take precedence over a diagnosis of AML, NOS, or MDS.

†Classify based on myeloblast percentage of all BM cells and of PB leukocytes and other MDS criteria.

Caso MC-48: lieve aumento degli eosinofili

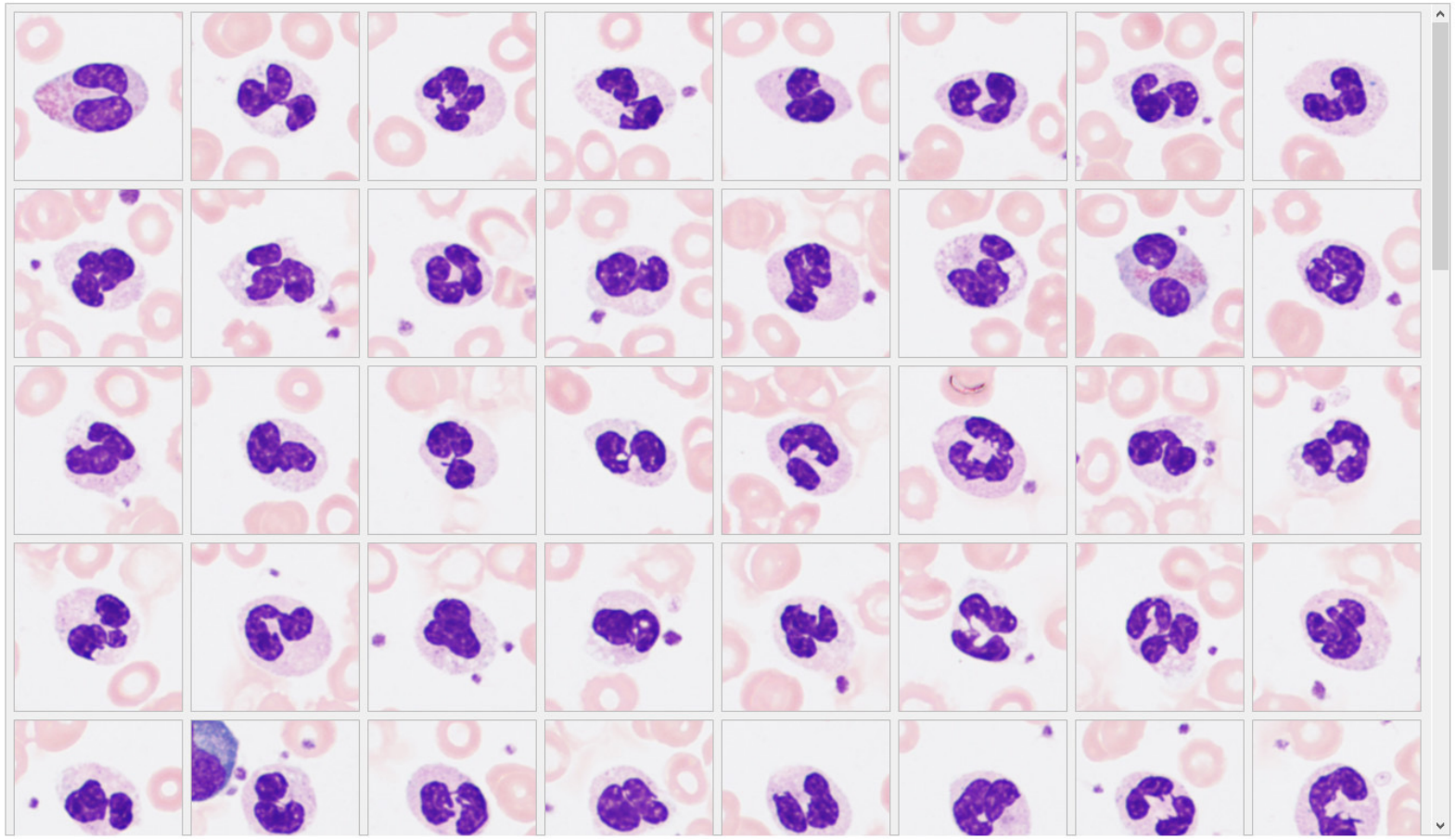
WBC | RBC | PLT

Nucleated cells&others

WBC (Total 200,100.0%)	Count	%
Unidentified		
Segmented neutrophils	119	59.5
Band neutrophils	14	7.0
L Lymphocytes	23	11.5
Monocytes	12	6.0
H Eosinophils	23	11.5
H Basophils	4	2.0
Metamyelocytes	1	0.5
Myelocytes	1	0.5
Promyelocytes	1	0.5
Blast cells	1	0.5
Reactive lymphocytes	1	0.5
Plasma		
Abnormal lymphocytes		
Abnormal promyelocytes		
Non-WBC (Total 28)	**Count**	**%**
Nucleated RBCs		
Giant platelets	1	

Comments

Segmented neutrophils(119,59.5%)



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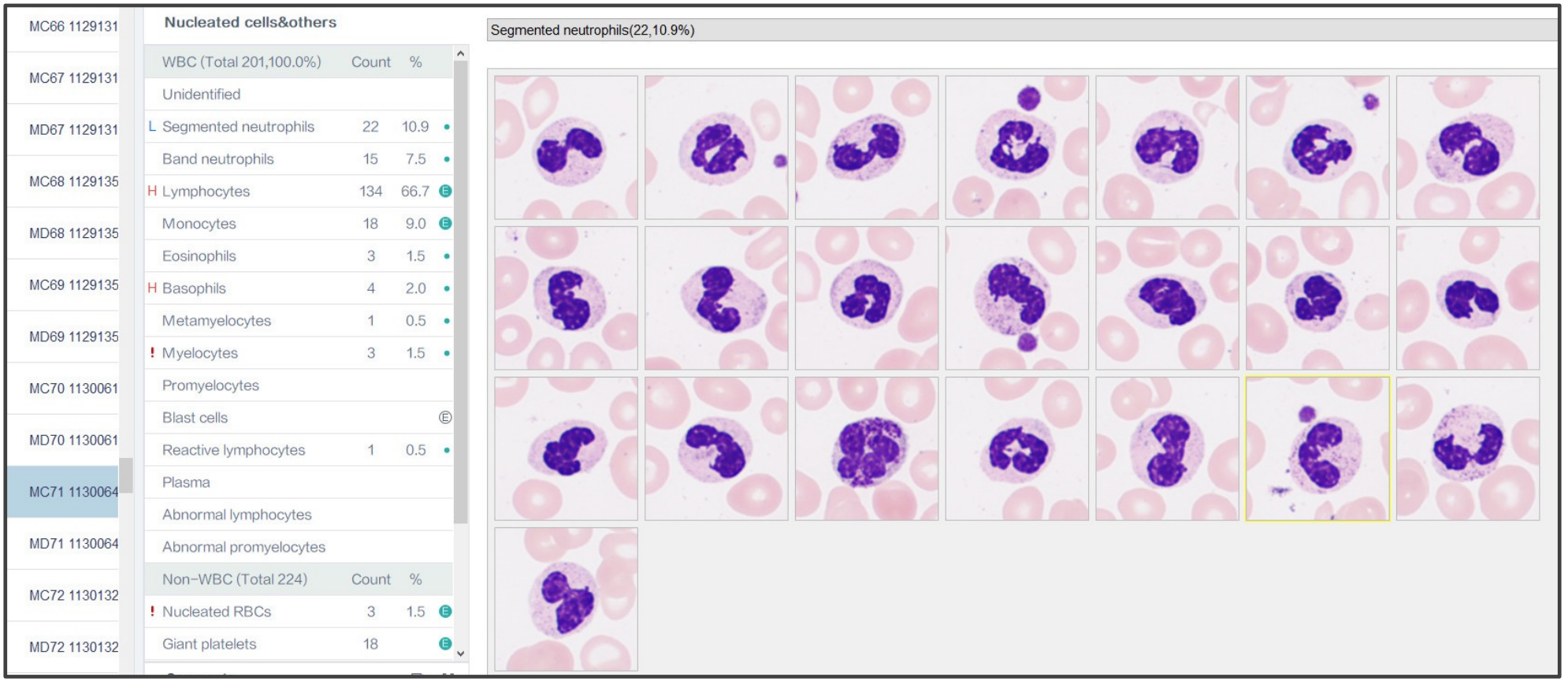
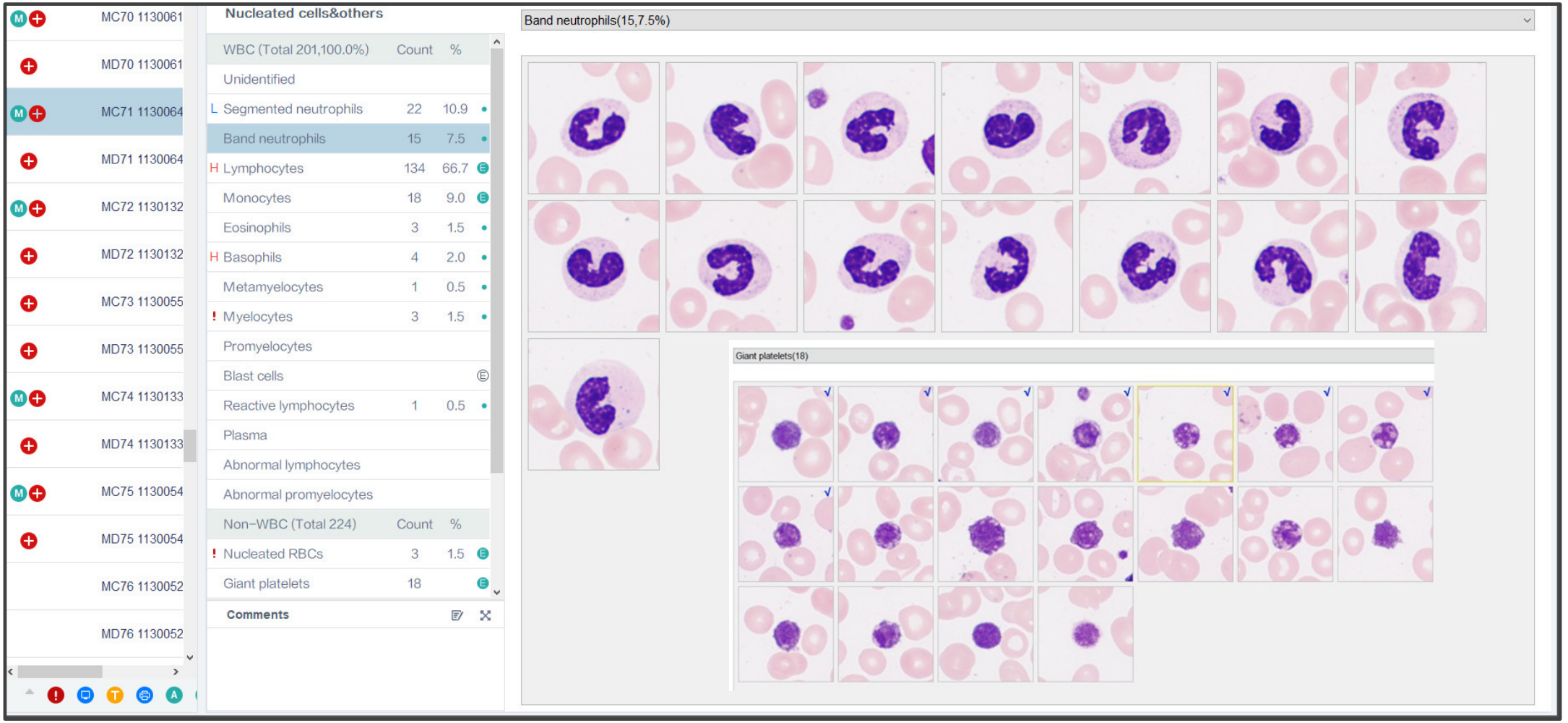
Caso MC-71 neutropenia (Neu)



Caso MC-71: neutropenia (Band & giant plt)



Caso MC-78: MDS follow up (Neu)

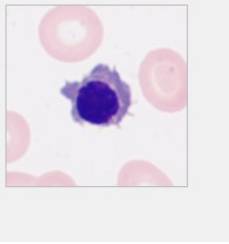
Sample ID
MD77 1130053
MC78 1130054
MD78 1130054
MC79 1130131
MD79 1130131
MC80 1130063
MD80 1130063
MC81 1130070
MD81 1130070
MC82 1201050601
MC83 1201053301
MC84 1201051501
MC85 1201051101

WBC | RBC | PLT

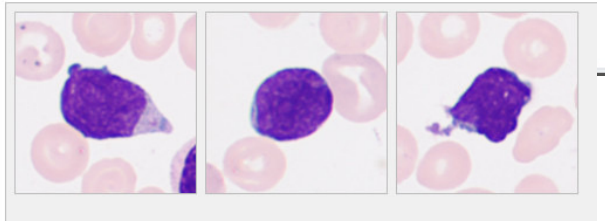
Nucleated cells&others

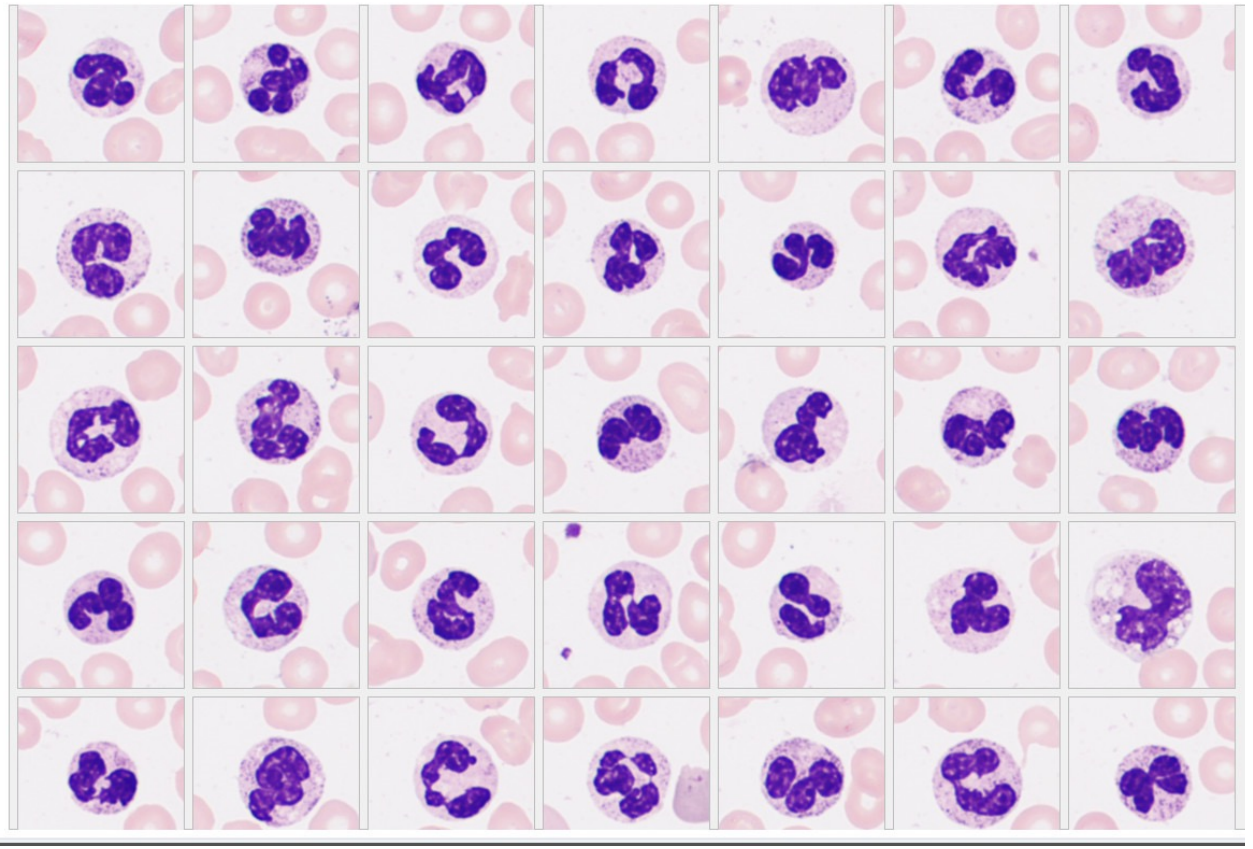
WBC (Total 202,100.0%)	Count	%
Unidentified		
Segmented neutrophils	114	56.4
Band neutrophils	8	4.0
L Lymphocytes	20	9.9
H Monocytes	42	20.8
Eosinophils		
Basophils		
Metamyelocytes	3	1.5
! Myelocytes	5	2.5
! Promyelocytes	7	3.5
! Blast cells	3	1.5
Reactive lymphocytes		
Plasma		
Abnormal lymphocytes		
Abnormal promyelocytes		
Non-WBC (Total 37)	**Count**	**%**
Nucleated RBCs	1	0.5
Giant platelets		

Nucleated RBCs(1,0.5%)



Blast cells(3,1.5%)



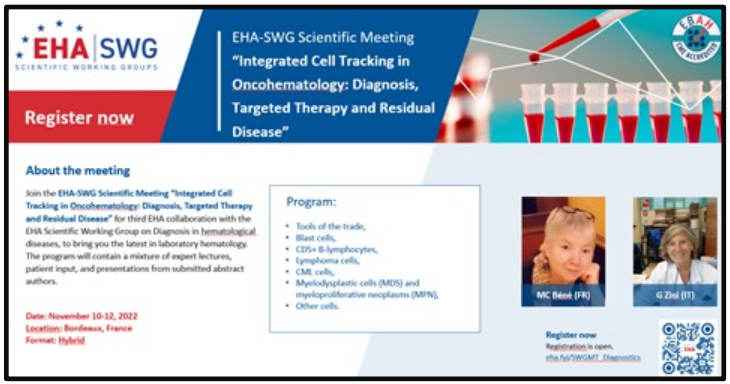


Prossimi appuntamenti morfologici

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Diagnosis in hematological diseases: Morphology and flow cytometry: T-cell proliferations
Hall Lehar 1-2

10. June 2022, 08:30 AM - 09:30 AM



Corso di perfezionamento in
DIAGNOSTICA EMATOLOGICA AVANZATA
I Edizione, aa.2022/2023

Direzione scientifica: Prof. Valerio De Stefano
Coordinamento didattico e scientifico: Prof.ssa Gina Zini

Martedì 27settembre - h17:20-18:20
Sessione Interattiva di Diagnostica Morfologica
R. Bain - G. Zini: «Morfologia in soccorso»