in collaborazione con:

Istituto Tumori "Giovanni Paolo II" IRCCS Bari

Agenzia Regionale per la Salute ed il Sociale Puglia

RTP REGISTRO TUMORI PUGLIA

XIX Corso di aggiornamento
per operatori dei registri tumori

GIST, sindromi mielodisplastiche, mielomi e linfomi e metodologie statistiche

BARI

6-8 novembre 2019
IRCCS Istituto Tumori
"Giovanni Paolo II"
viale Orazio Flacco, 65 Bari

Sindromi Mielodisplastiche e Mieloma: conoscere i diversi percorsi diagnostici

Giorgina Specchia

In Ematologia…….

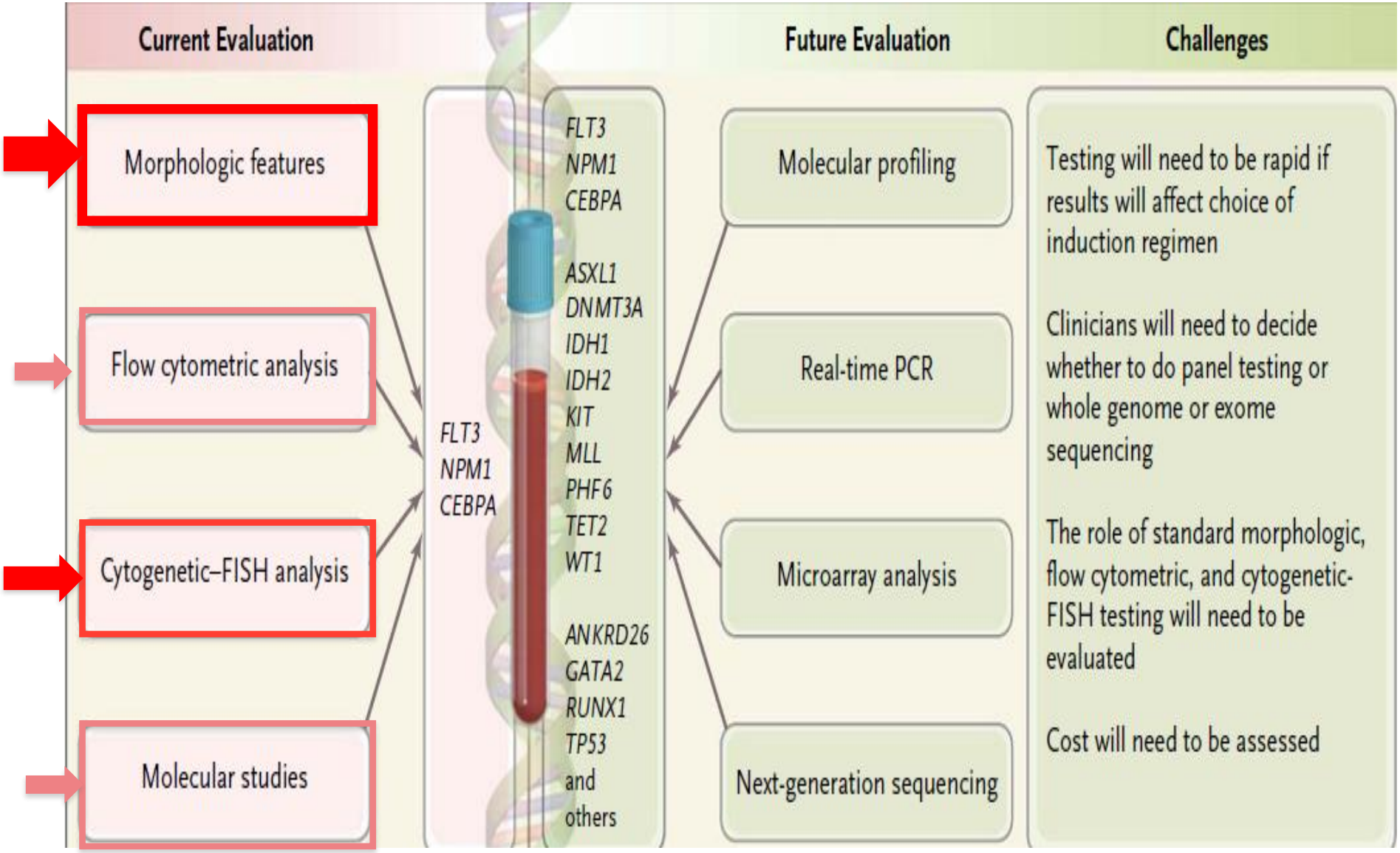
- ✓ **Indagini Fondamentali per la Diagnosi !!!**

- ✓ Indagini Necessarie per lo score Prognostico

Appropriatezza Dx in Ematologia

- WHO 2008-2016
- Linee Guida/ELN
- PDTA/LEA

Diagnostica in Ematologia



ELN 2010/2013

Sindromi Mielodisplastiche (SMD)

 # PATOLOGIE CLONALI ACQUISITE della CELLULA STAMINALEPLURIPOTENTE , CARATTERIZZATE da MIDOLLO IPERCELLULARE e da PANCITOPENIA PERIFERICA

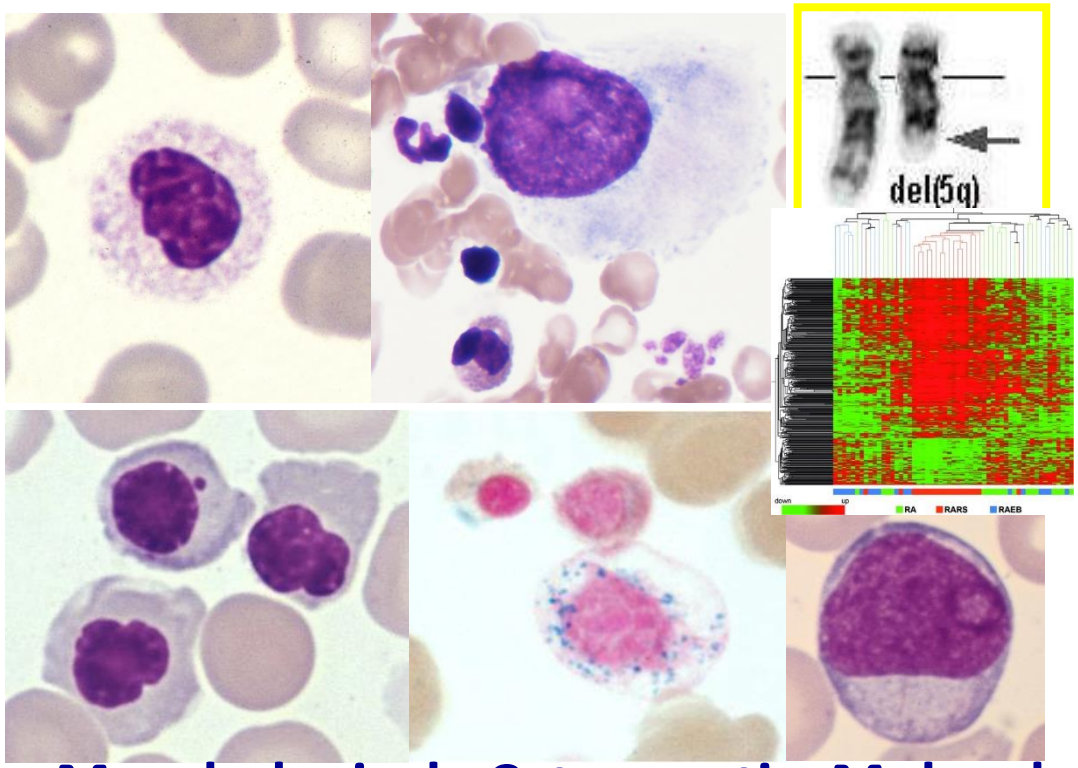
#ALTERAZIONE dei MECCANISMI di Regolazione della EMOPOIESI (proliferazione e differenziazione dei progenitori emopoietici)

#EVOLUZIONE in LEUCEMIE ACUTE

#FREQUENTI nei SOGGETTI ANZIANI

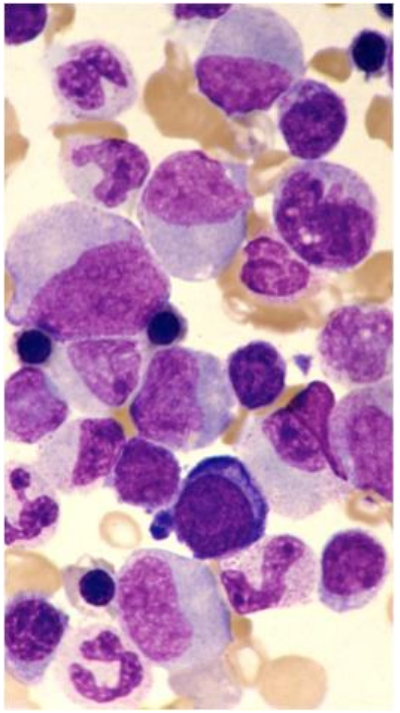
Myelodysplastic Syndromes / Neoplasms

Clonal haematopoietic stem cell diseases characterized by Cytopenia(s), Dysplasia, **Ineffective Haematopoiesis**, increased Risk of development of AML

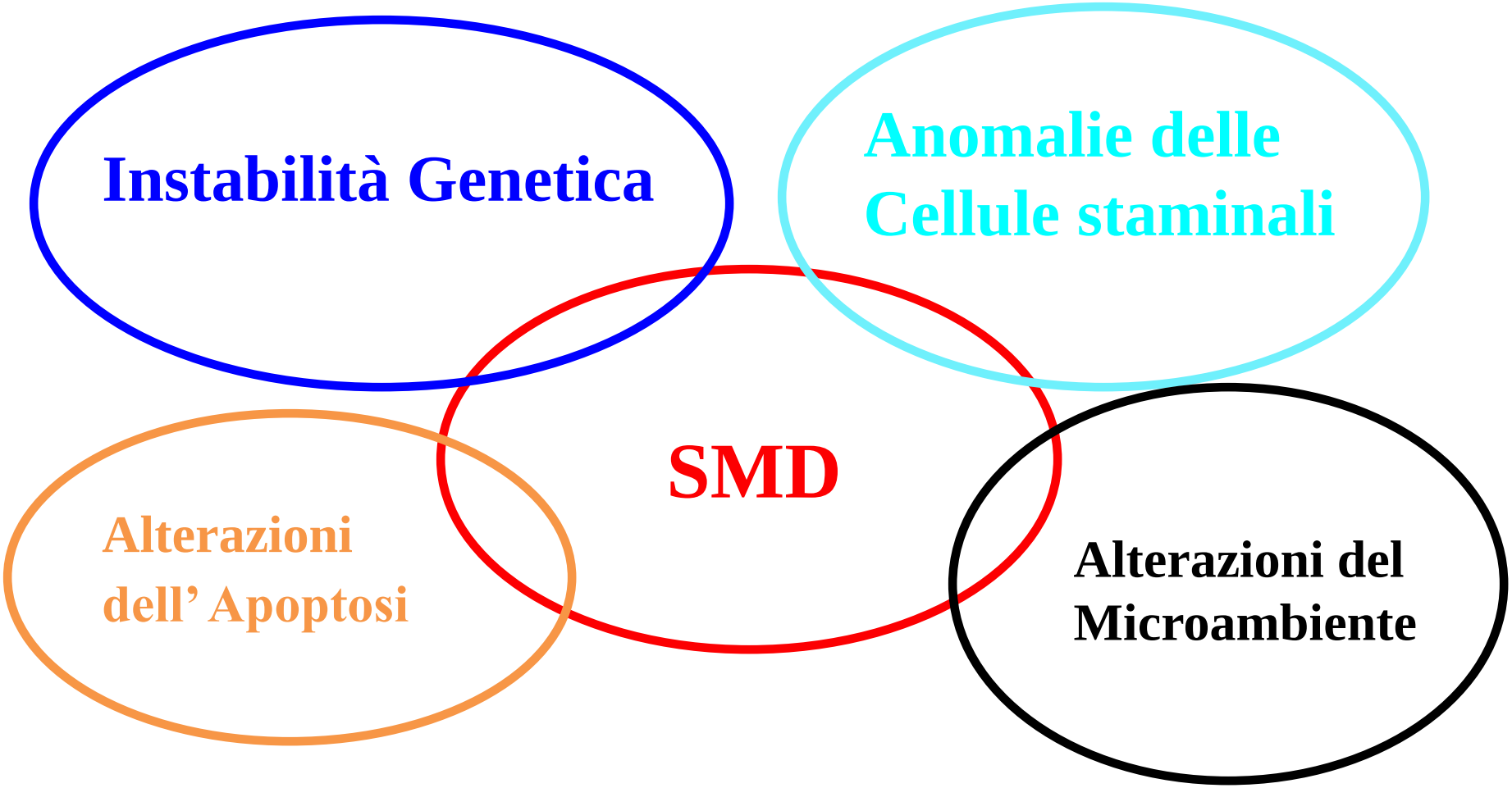


Morphological , Cytogenetic, Molecular Findings

Progression to AML (25-30%)



PATOGENESI



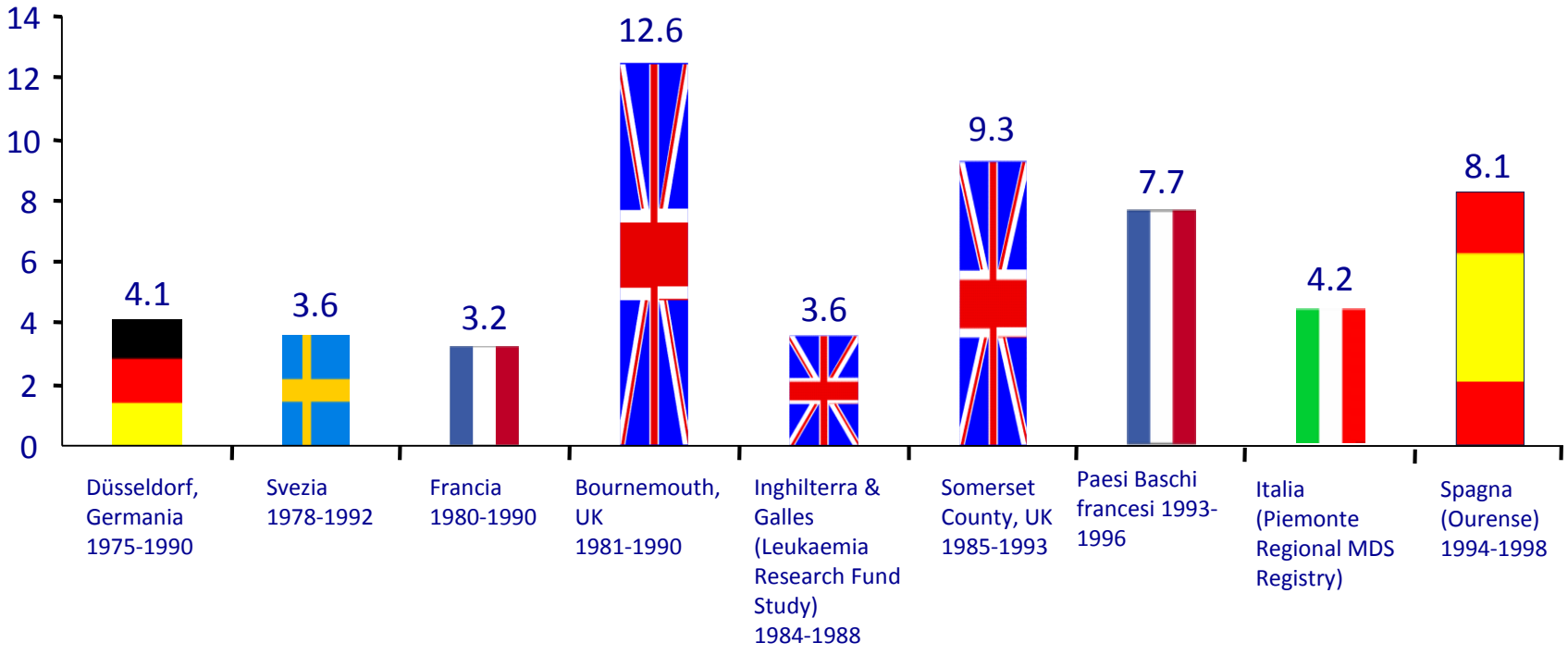
La patogenesi delle SMD è complessa e coinvolge numerose vie che regolano la proliferatione, maturazione e sopravvivenza cellulare

Epidemiologia

- 15,000–25,000 nuovi casi/anno negli USA
- ~25,000 nuovi casi/anno in EU
- Incidenza media in EU 1975–1996: Circa 4,4 cases per 100.000 persone/anno
- Età mediana >60 (70% >50 anni)
- M > F

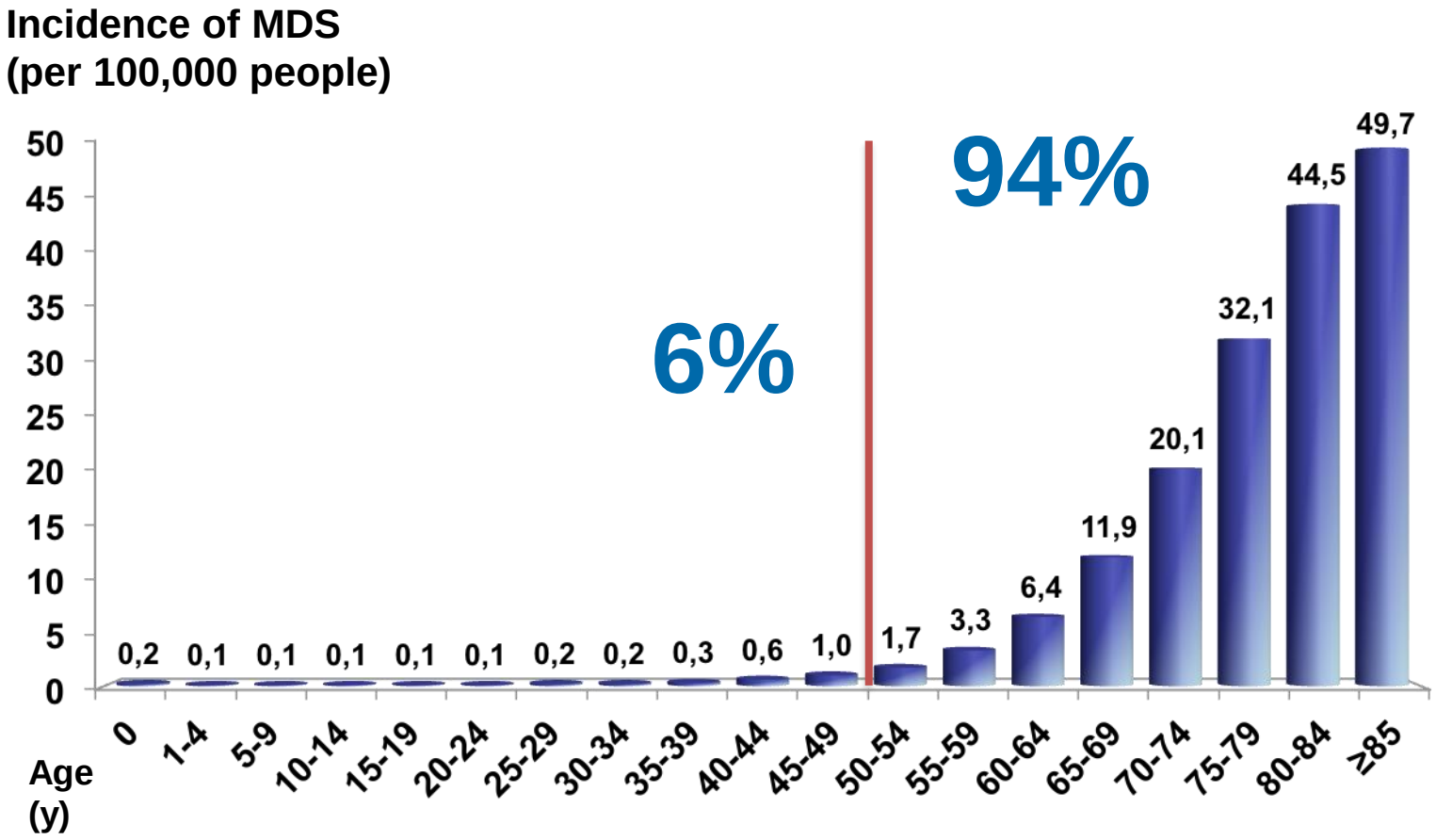
Derived from Hamblin TJ. Epidemiology of MDS. In: Bennett JM (ed). MDS: Pathobiology and Clinical Management. New York: Marcel Dekker Inc.;2002

Incidenza in EU per 100.000 persone



Adapted from Hamblin TJ. Epidemiology of MDS. In: Bennett JM (ed). In: MDS: Pathobiology and Clinical Management. New York: Marcel Dekker Inc.; 2002, and MDS: Pathobiology and Clinical Management, page 18, by Hamblin TJ. Courtesy of Marcel Dekker,Inc.
http://www.mds.piemonte.it
Iglesias Gallego M et al. Haematologica 2003;88(10):1197–1199

Epidemiologia delle MDS



Estimated incidence in the USA is >10,000/yr;

MDS is prevalent in the elderly (> 60 yrs old, 86%)

MA X, et al, Am J Med. 2012.

Eritropoiesi inefficace → **Anemia**

Granulocitopoiesi inefficace → **Neutropenia**

Megacariocitopoiesi inefficace → **Piastrinopenia**

CLINICA

Anemia → **Astenia, Dispnea, Cardiopalmo…..**

Neutropenia → **Infezioni (Febbre, Broncopolmoniti, Ascessi, Infezioni vie urinarie)**

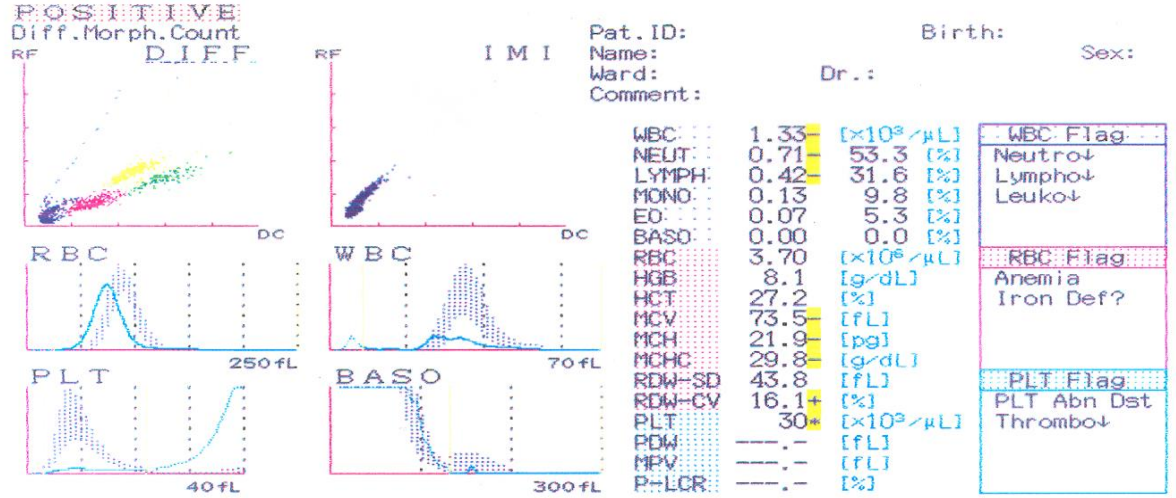
Piastrinopenia → **Manifestazioni emorragiche (ecchimosi, petecchie, gengivorragie….)**

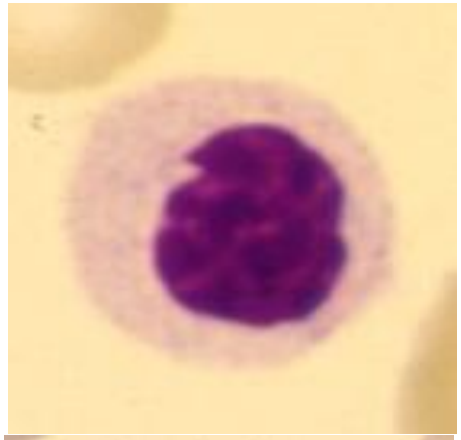
PERCORSO DIAGNOSTICO……..

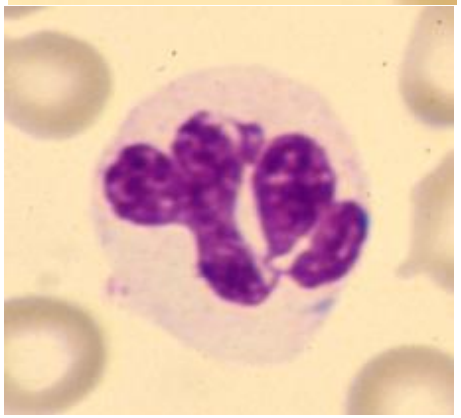
- **Anamnesi !!**
- **Emocromo-Reticolociti**
- **Es. morfologico s. periferico**
- **Es. morfologico s. midollare (+ Pearls)**
- **Citogenetica/FISH**
- **Biopsia Osteomidollare***
- s-EPO
- Assetto marziale
- HLA*
- ……

Diagnosi SMD

Clinica - -

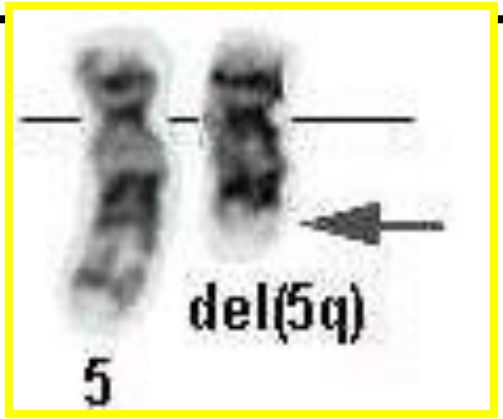






Emocromo

Midollo



Morfologia
Citochimica
Cariotipo
……

Clinica ++

Quando sospettare una mielodisplasia ……

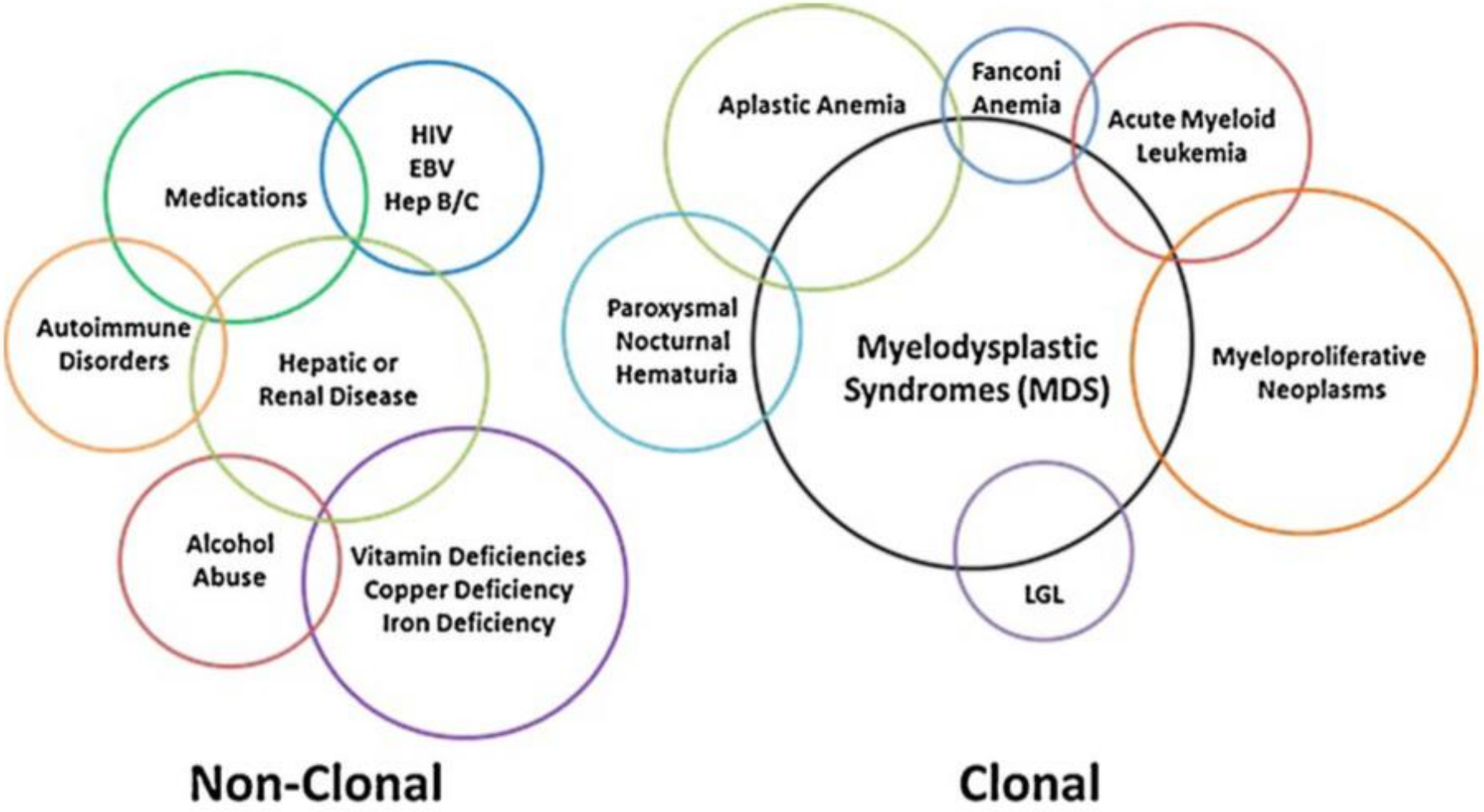
Fattori facilmente associati a diagnosi di SMD

- ✓ **Età avanzata**
- ✓ **Anemia che abbia le seguenti caratteristiche**
  - **iporigenerativa (reticolociti bassi)**
  - **macrocitica (MCV elevato)**
- ✓ **Anemia associata ad altra citopenia**
- ✓ **Anomalie morfologiche della serie granulocitaria((ipogranularità,pseudo-Pelger, ecc.), megacariocitaria**

Diagnosi Differenziale

- ✓ Anemia Aplastica-EPN
- ✓ Disordini Nutrizionali (Anemia Megaloblastica)
- ✓ Alterazioni citomorfologiche da Alcolismo
- ✓ Infezioni virali (HBV, HCV, CMV,Parvovirus B19,HIV, etc)
- ✓ Sostanze tossiche (antibiotici,chemioterapici, piombo, benzene)
- ✓ Anemia dell'anziano non altrimenti definita
- ✓ Epatopatie
- ✓ Patologie Autoimmuni
- ✓ ……

CYTOPENIAS



….the diagnosis of **Cytopenias** remains a **core task** of hematology clinical practice……..

Bejar, Curr Hematol Malig Rep 2015

Curr Hematol Malig Rep (2012) 7:310–320

Dysplasia Has A Differential Diagnosis: Distinguishing Genuine Myelodysplastic Syndromes (MDS) From Mimics, Imitators, Copycats and Impostors

David P. Steensma

Minimal Diagnostic Criteria for MDS as Proposed by 2006 Vienna Workshop [12•]

Both "prerequisite criteria" are necessary to make the diagnosis of MDS:

1) Marked cytopenia (i.e., hemoglobin <11 g/dL, absolute neutrophil count $<1.5\times10^9$/L, or platelets $<100\times10^9$/L) in at least one lineage lasting for ≥6 months, unless cytogenetic studies reveal MDS,

2) Exclusion of another clonal or non-clonal hematopoietic disease or non-hematopoietic disease

At least **one of three "decisive criteria"** is also required (but see below):

1) Morphologic dysplasia in at least 10 % of all cells in one or more of the major cell lineages in the bone marrow aspirate,

2) A typical MDS-associated cytogenetic abnormality (e.g., del(5q), monosomy 7)

3) Marrow blast cell proportion 5–19 %.

There are also **two "co-criteria"** for patients who meet both "prerequisite" criteria but none of the "decisive" criteria; at least one must be met:

1) Abnormal marrow immunophenotype by flow cytometry that is compatible with a diagnosis of MDS according to European Leukemia Network criteria

2) Evidence of a monoclonal cell population based on either a human androgen receptor assay, gene chip analysis, or mutation analysis.

MDS: Differential Diagnosis

Other Neoplasms :MDS/MPN…..

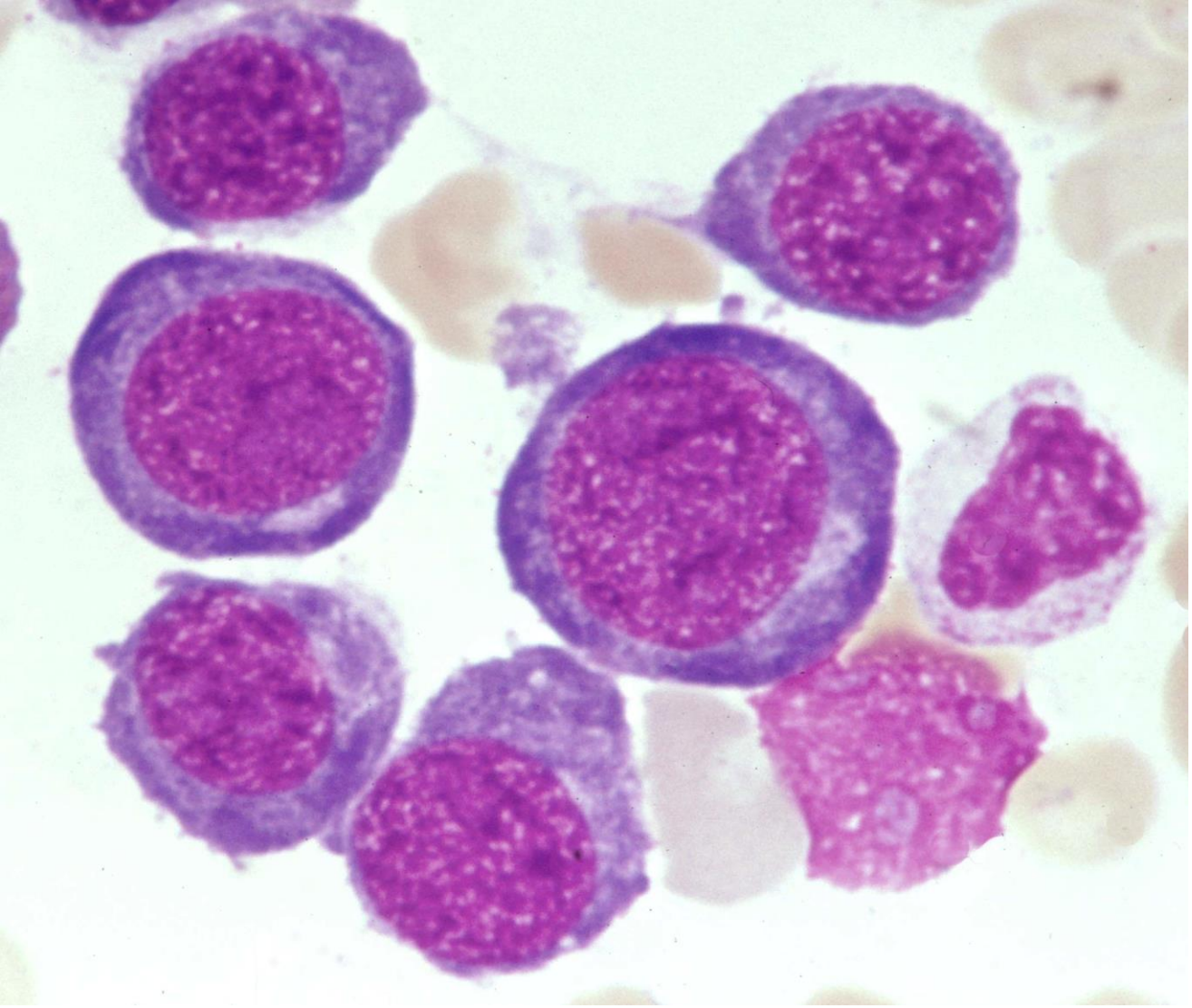
Congenital Syndromes:Fanconi Anemia…

Immune Disorders : SAA,ITP,PRA……

Nutritional Deficiencies :B12, Folate…..

Reactive Conditions or Infections: HIV,

Alcohol,Drugs…….

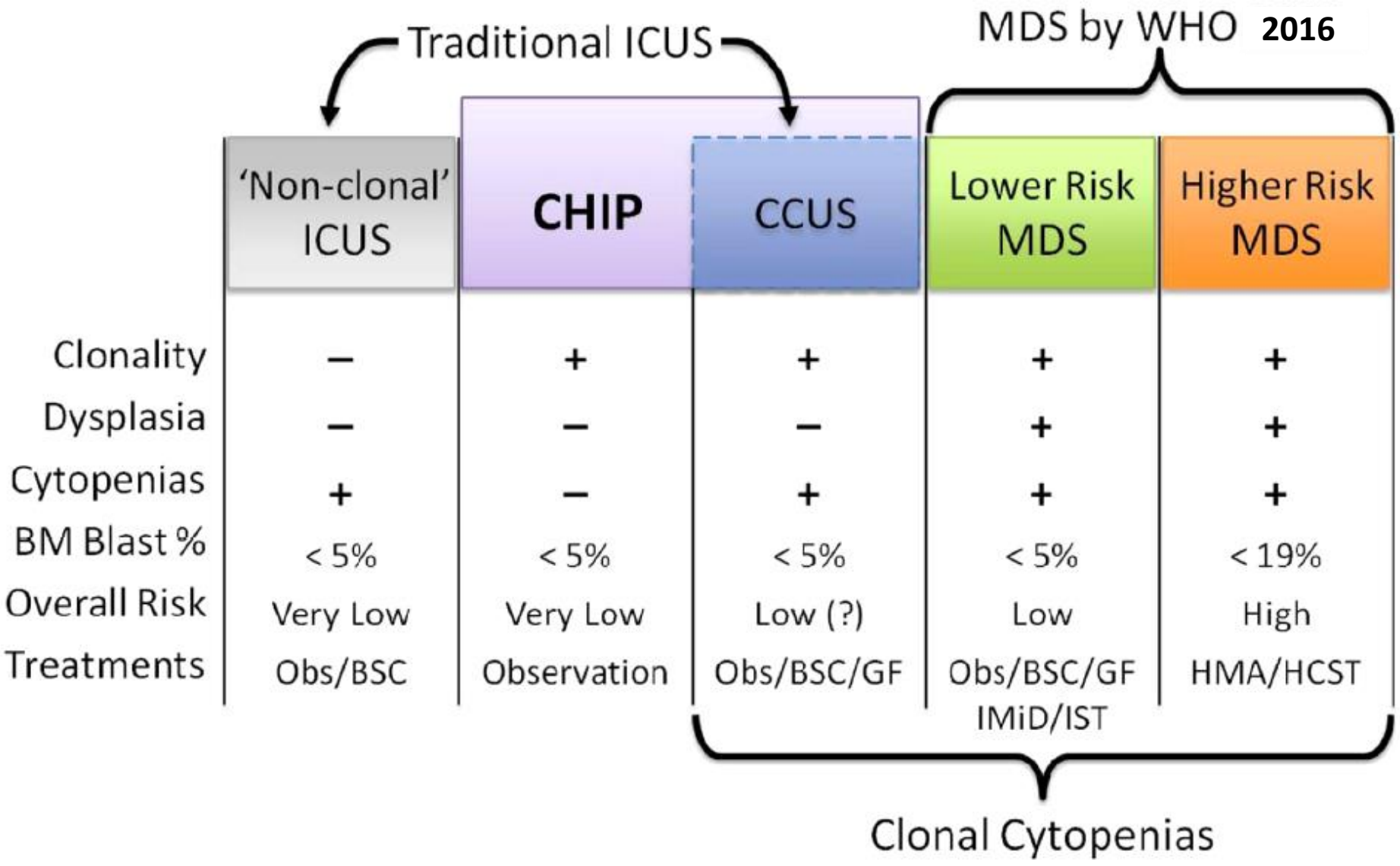


C .A. 41 y

Hb 4.5gr/dl
ANC 1.5×10^9/L
Plt 90×10^9 /L

Cobalamin 150 pg/ml

Megaloblastic Anemia



Steeensma et al., Blood 2015

PERCORSO DIAGNOSTICO……..

- **Anamnesi !!**
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- **Es. morfologico s. periferico**
- **Es. morfologico s. midollare con Perls**
- **Citogenetica/FISH**
- **Biopsia Osteomidollare***
- s-EPO
- Assetto marziale
- HLA*
- ……

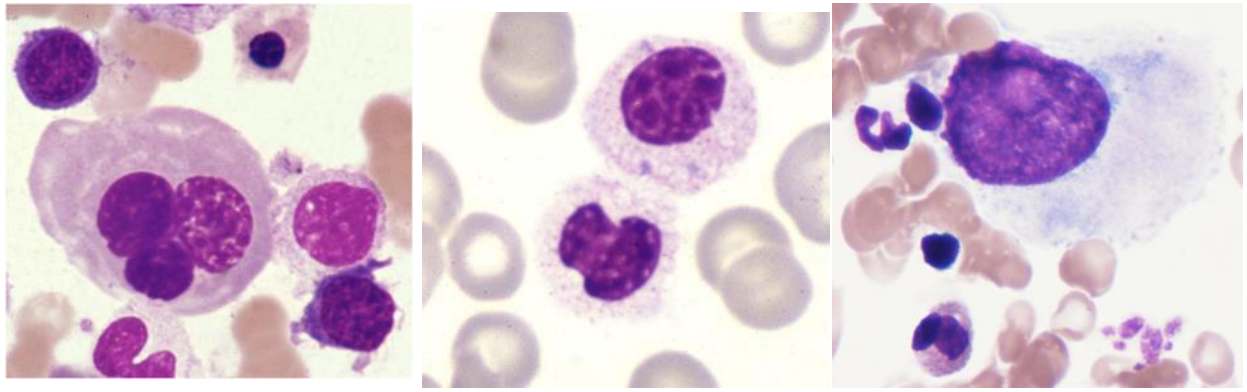
Per la Diagnosi di SMD

- **E' indispensabile** rilevare una displasia in > 10% delle cellule della linea mieloide /eritroide/megacariocitaria
- **E' necessario** contare i blasti nel SP e MI
- **E' fondamentale** effettuare l'analisi cariotipica (normale però nel 40-50% circa dei casi !!)
- **E' importante** ,soprattutto nei casi senza evidenza di anomalie cromosomiche e con displasia modesta monitorare il paziente (SMDI ? o altro ?)

Diagnosis of MDS 2016 → 2018

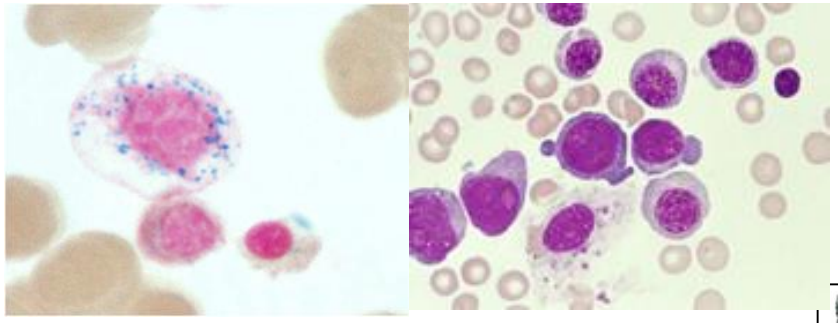
Peripheral Cytopenia

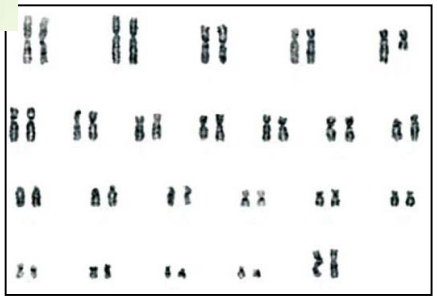
Dysplasia



Sideroblasts

Blasts





Clonal cytogenetic abnormalities Gene Mutations : SF3B1, ASXL1, TP53……..

Classificazioni delle SMD

FAB	WHO 2008
Anemia refrattaria	▪ Anemia refrattaria ▪ Citopenia con displasia multilineare ▪ Sindrome mielodisplastica inclassificabile ▪ Sindrome mielodisplastica con isolata del (5q)
Anemia refrattaria con sideroblasti ad anello	▪ Anemia refrattaria con sideroblasti ad anello ▪ Citopenia con displasia multilineare e sideroblasti ad anello
Anemia refrattaria con eccesso di blasti	▪ Anemia refrattaria con eccesso di blasti - 1 ▪ Anemia refrattaria con eccesso di blasti – 2
Anemia refrattaria con eccesso di blasti in trasformazione	▪ Leucemia Acuta Mieloide
Leucemia Mielomonocitica Cronica	▪ Neoplasia mielodisplastica/Mieloprolifertiva

WHO classification of tumours of haematopoietic and lymphoid tissues; International Agency for Research on Cancer

blood®
2016 127: 2391-2405
doi:10.1182/blood-2016-03-643544 originally published online April 11, 2016

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

Daniel A. Arber, Attilio Orazi, Robert Hasserjian, Jürgen Thiele, Michael J. Borowitz, Michelle M. Le Beau, Clara D. Bloomfield, Mario Cazzola and James W. Vardiman

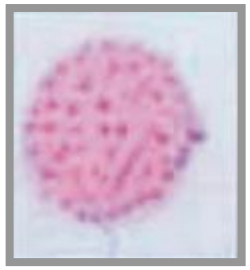
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood

Diseritropoiesi

Sangue periferico

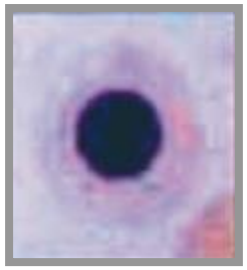
Anisocitosi

Poichilocitosi



Punteggiatura basofila

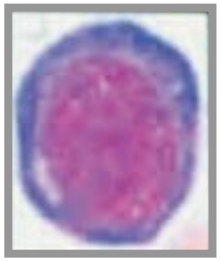
Corpi di Howell-Jolly



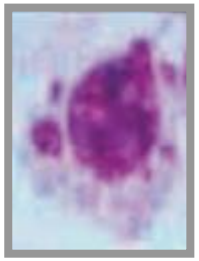
Elementi nucleati

Macrocitosi

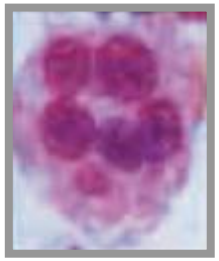
Midollo osseo



Megaloblastosi



Frammenti nucleari



Multinuclearità

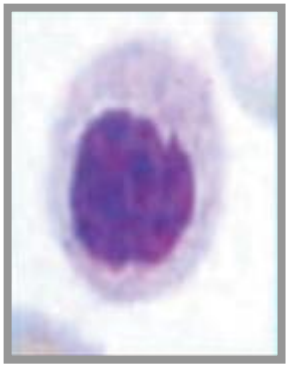
Forma anomala del nucleo

Ponti internucleari

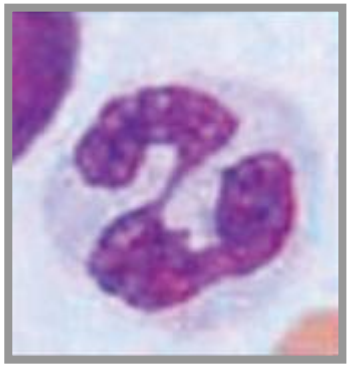
Anomalie citoplasmatiche

Sideroblasti ad anello

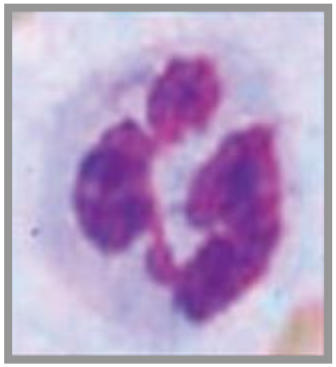
Disgranulopoiesi



Pseudo-anomalia di Pelger-Huet



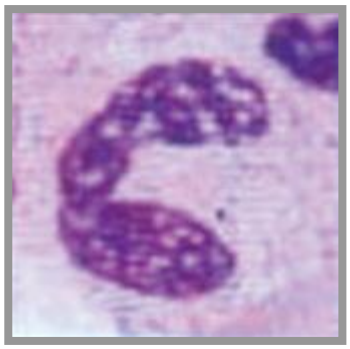
Citoplasma ipogranulare



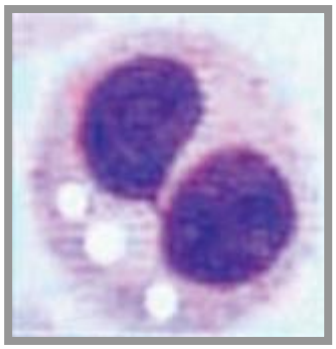
Corpi di Dhole

“Sticks” nucleari

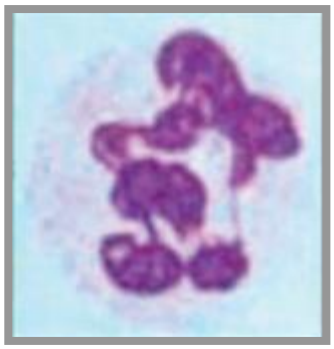
Anomalie della positività perossidasica



“Clumping” cromatinico



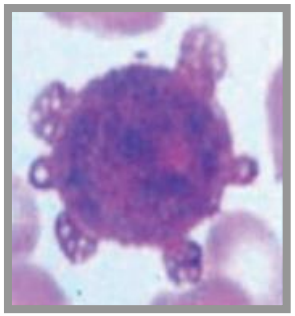
Vacuoli citoplasmatici



Ipersegmentazione nucleare

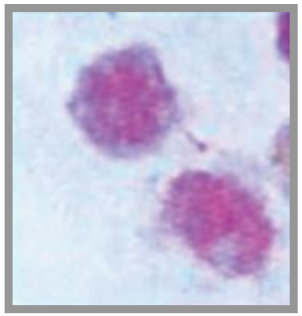
Distrombocitopoiesi

Sangue periferico



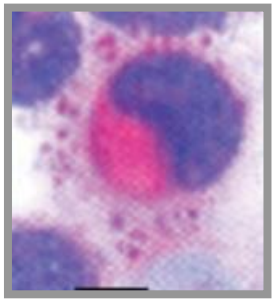
Piastrina gigante

Piastrina ipogranulare

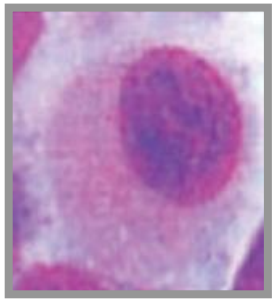


Megapiastrine

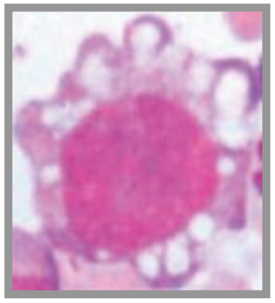
Midollo osseo



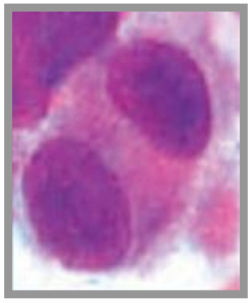
Micromegacariocito



Megacariocito mononucleato



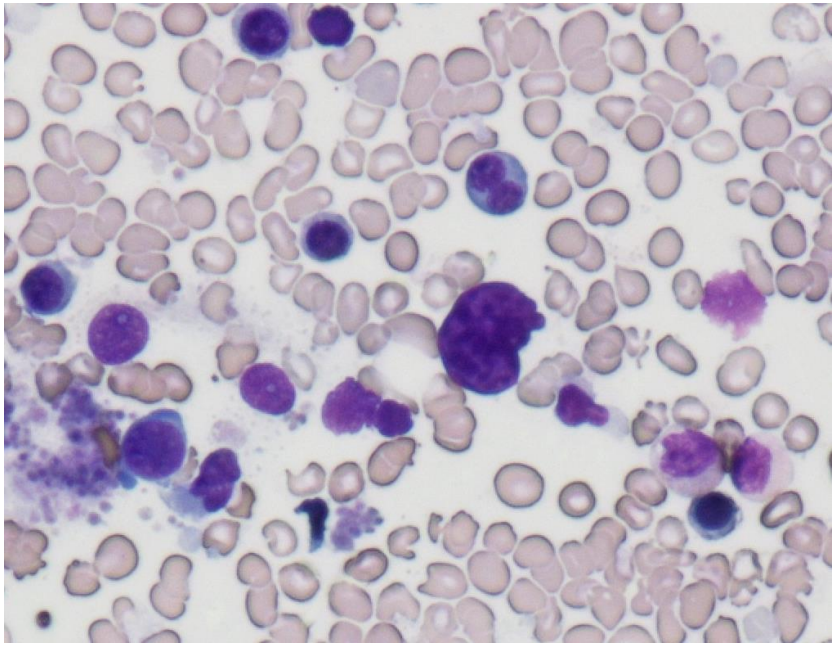
Megacariocito con alterazioni citoplasmatiche

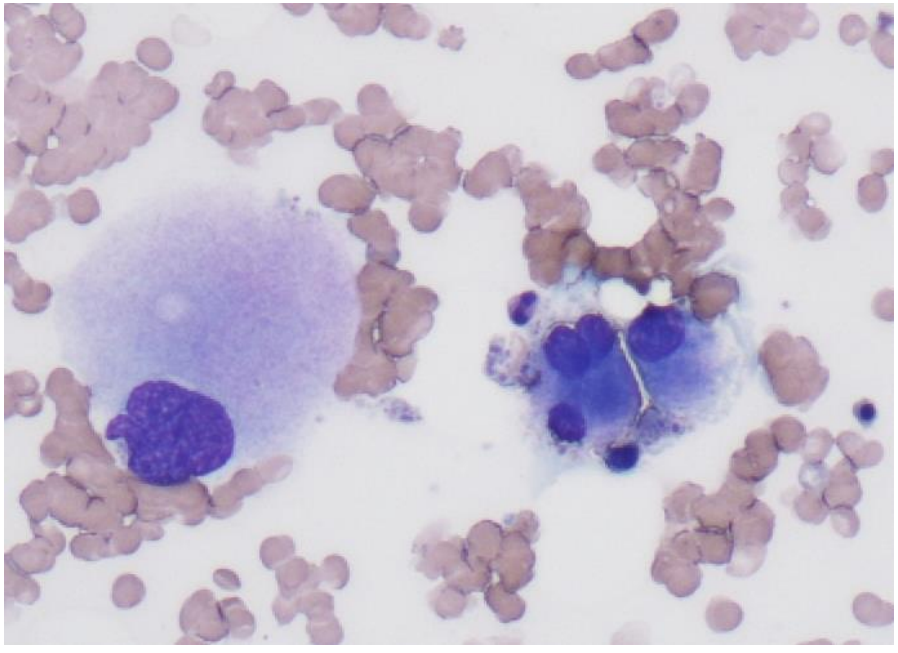


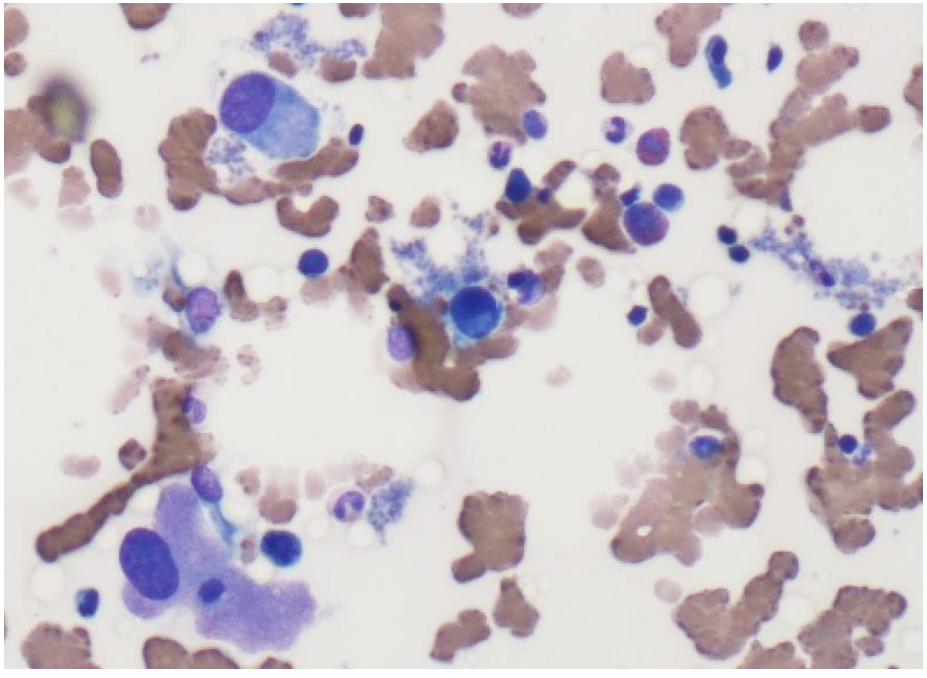
Megacariocito binucleato

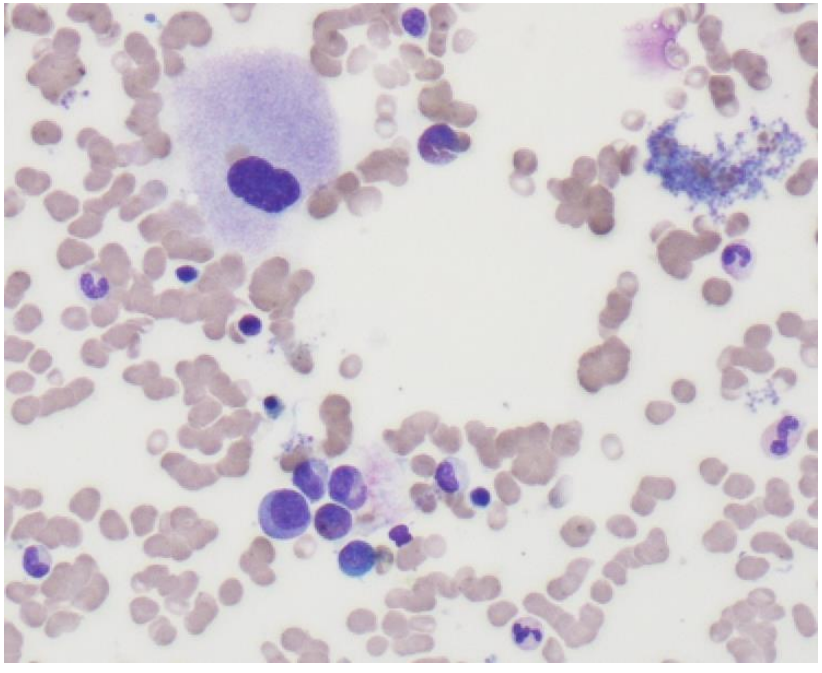
Utilità della Biopsia Osteo-Midollare (BOM) nelle SMD

- Valutazione della reale **cellularità** midollare
- **Topografia** delle cellule emopoietiche
- Valutazione della **fibrosi** (colorazione per il reticolo)
- Valutazione della **componente non emopoietica(Carcinosi)**



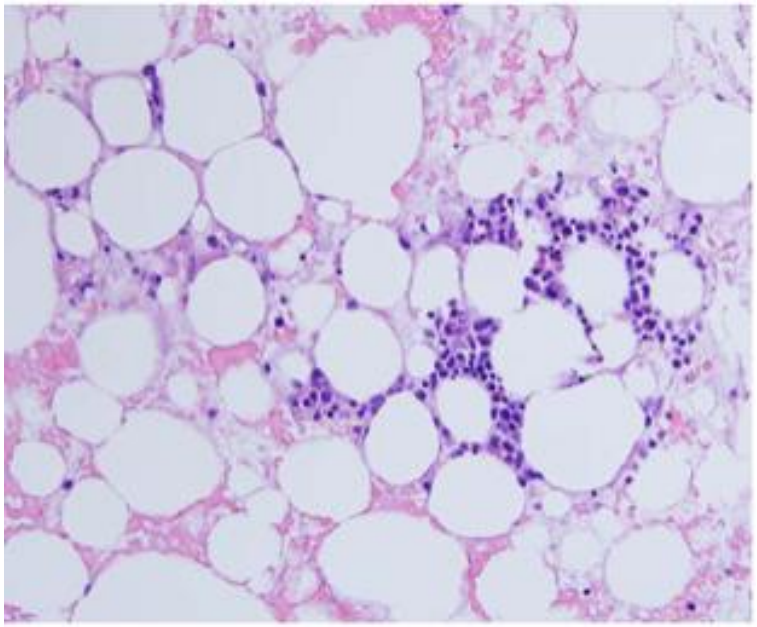


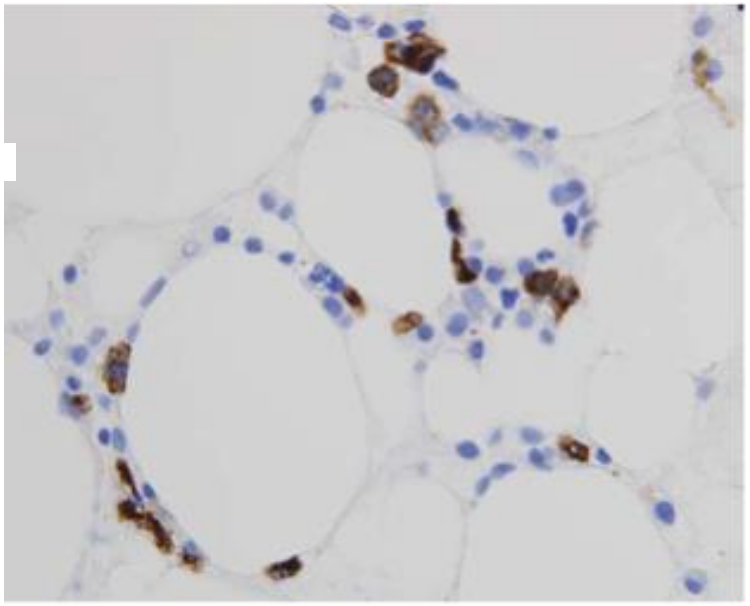


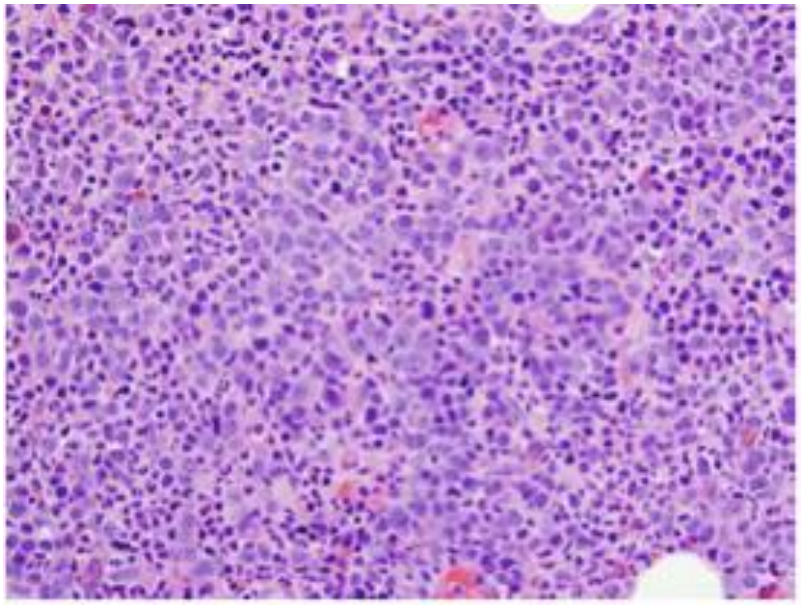


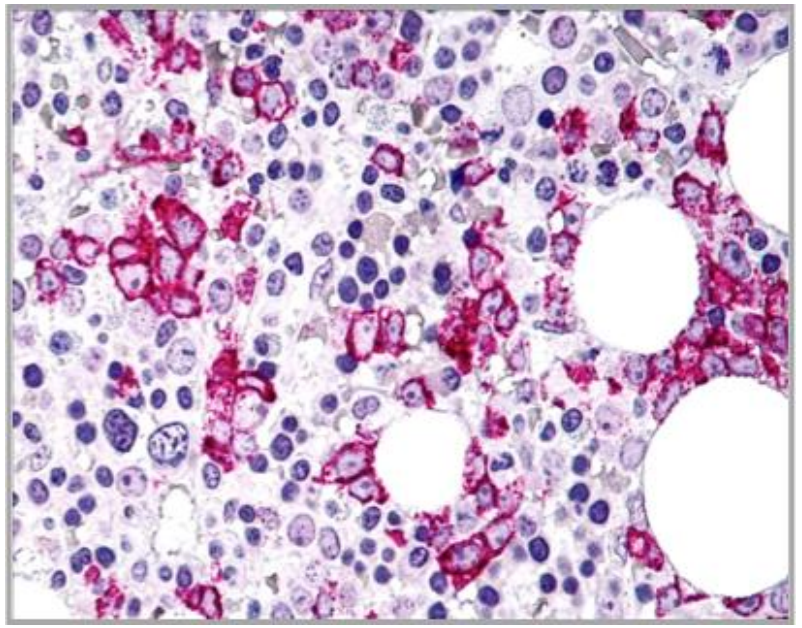
HYPOPLASTIC MDS

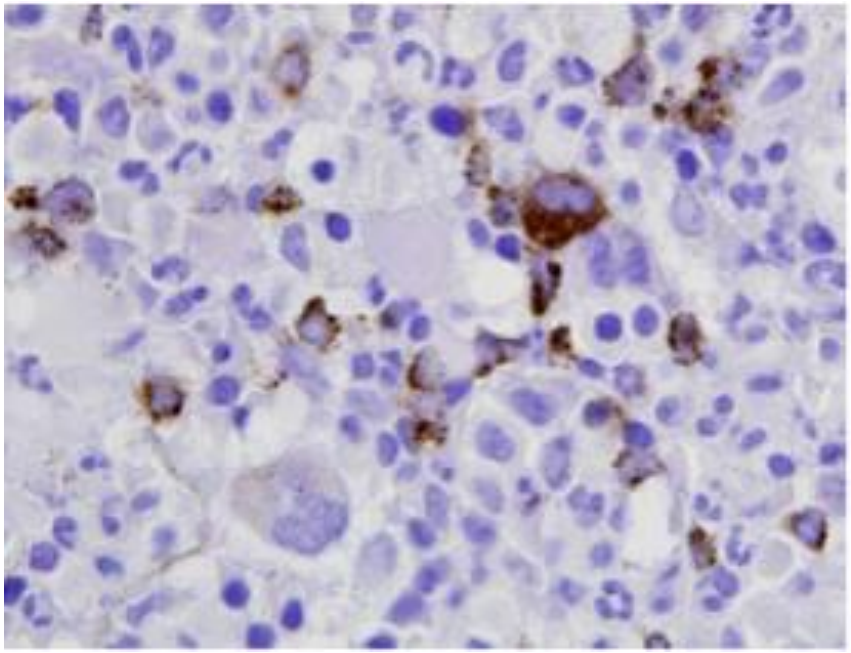
Hypoplastic MDS (h-MDS) is defined by low marrow cellularity (cellularity of less than 20% for patients older than 70 years of age and less than 30% for individuals younger than 70 years), vary-

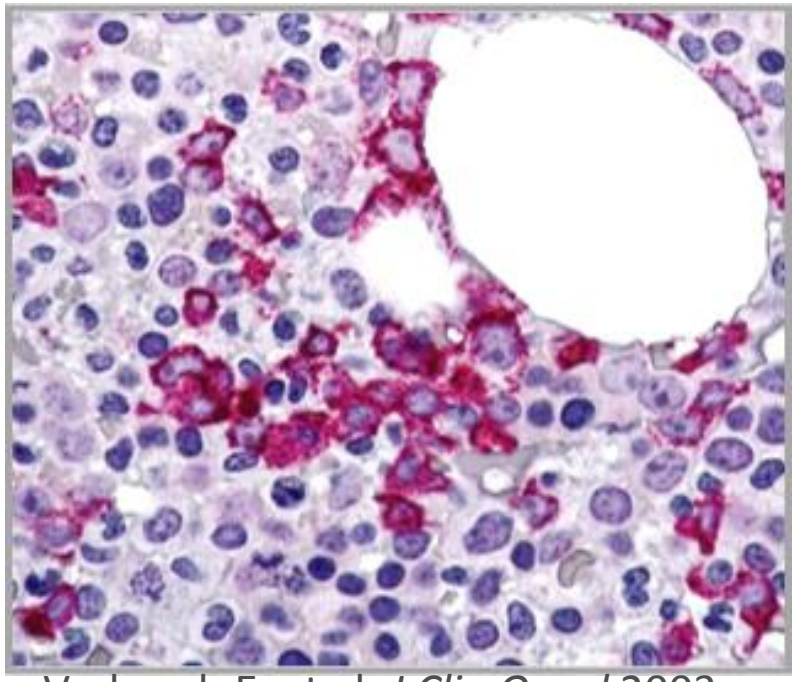












Czader et al. Current Pharmaceutical Design 2012

Verburgh E, et al. *J Clin Oncol* 2003

Anemia Refrattaria

Pe

✓Eritrociti normocromici e normocitici

oppure

✓Eritrociti normocromici e microcitici

✓Neutrofili e piastrine normali

✓Mieloblasti <1%

MO

✓Diseritropoiesi leggera o moderata con alterazioni del nucleo

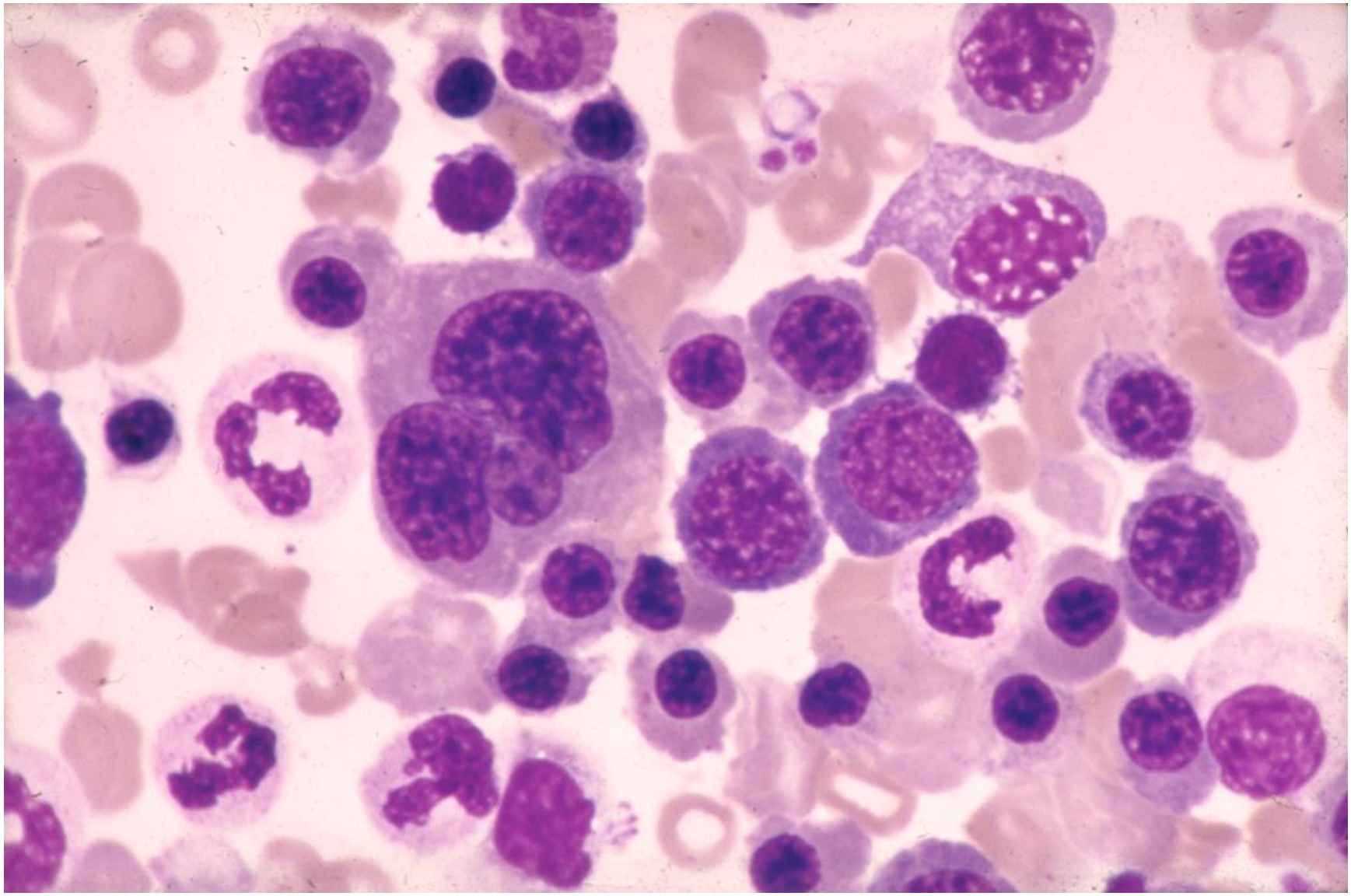
✓Sideroblasti ad anello <15% dei precursori eritroidi

✓Neutrofili e megacariociti normali o con displasia minima

✓Mieloblasti <5%

✓BOM: iperplasia eritroide

Anomalie citogenetiche (25% dei casi): del(20q), +8, -5 e/o -7



Del (20q) / Del(5q)/-7,Del(7q)

Anemia Refrattaria con sideroblasti ad anello

MO

✓Iperplasia e displasia eritroide

✓Sideroblasti ad anello >15% dei precursori eritroidi
(10 o più granuli di ferro circondano 1/3 o più del nucleo)

✓Lobature nucleari e caratteristiche megaloblastoidi

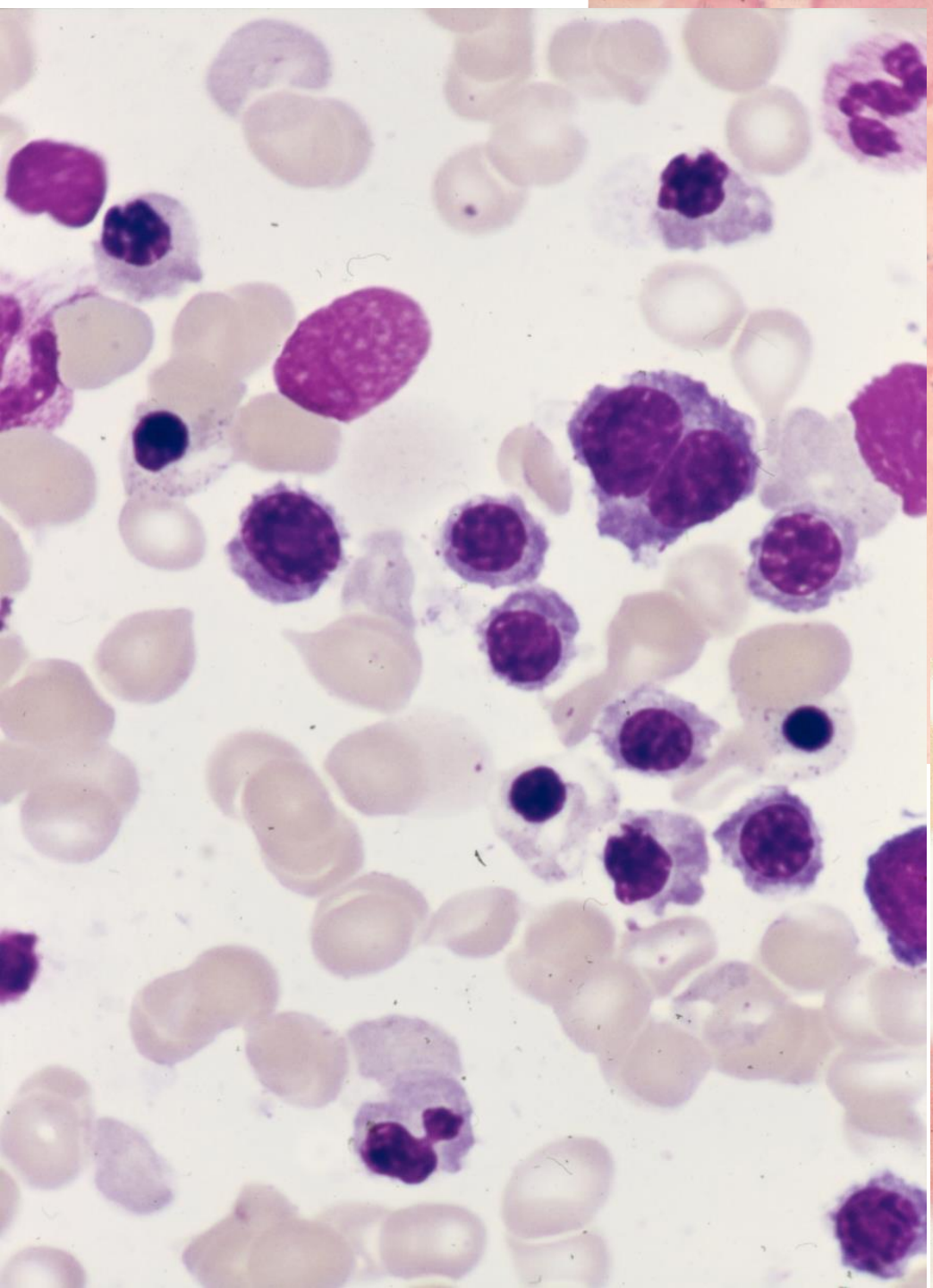
✓Neutrofili e megacariociti normali

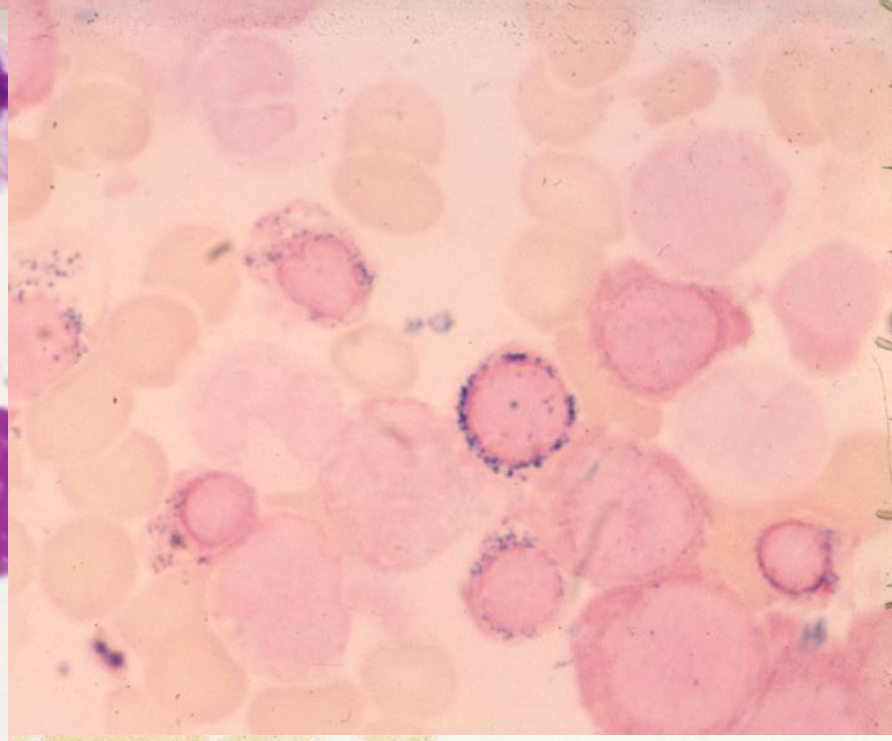
✓Macrofagi carichi di emosiderina

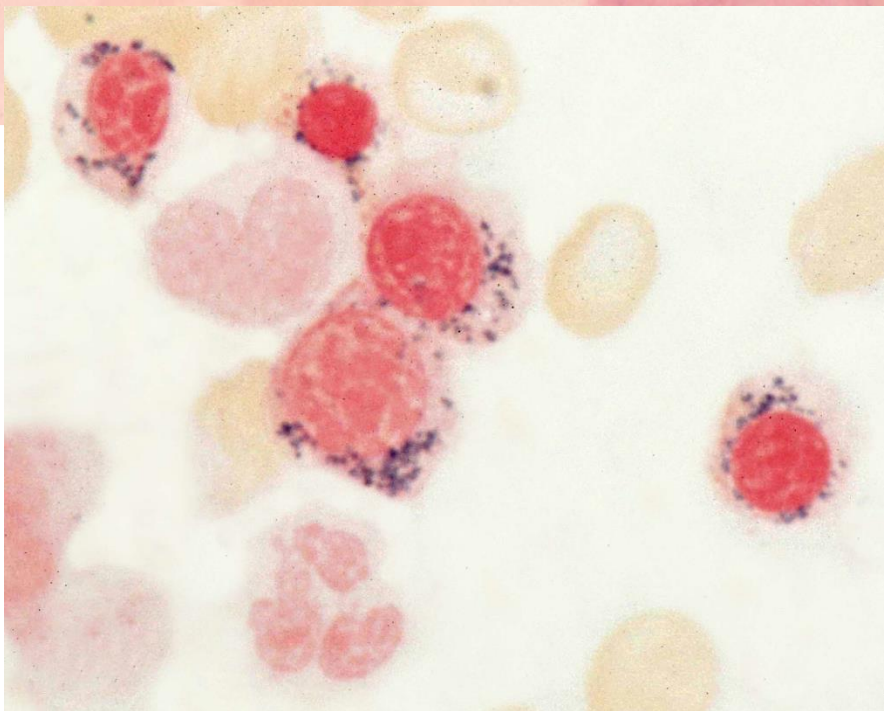
✓Mieloblasti <5%

✓BOM: normocellulare o marcatamente ipercellulare

Anomalie citogenetiche: <10% dei casi





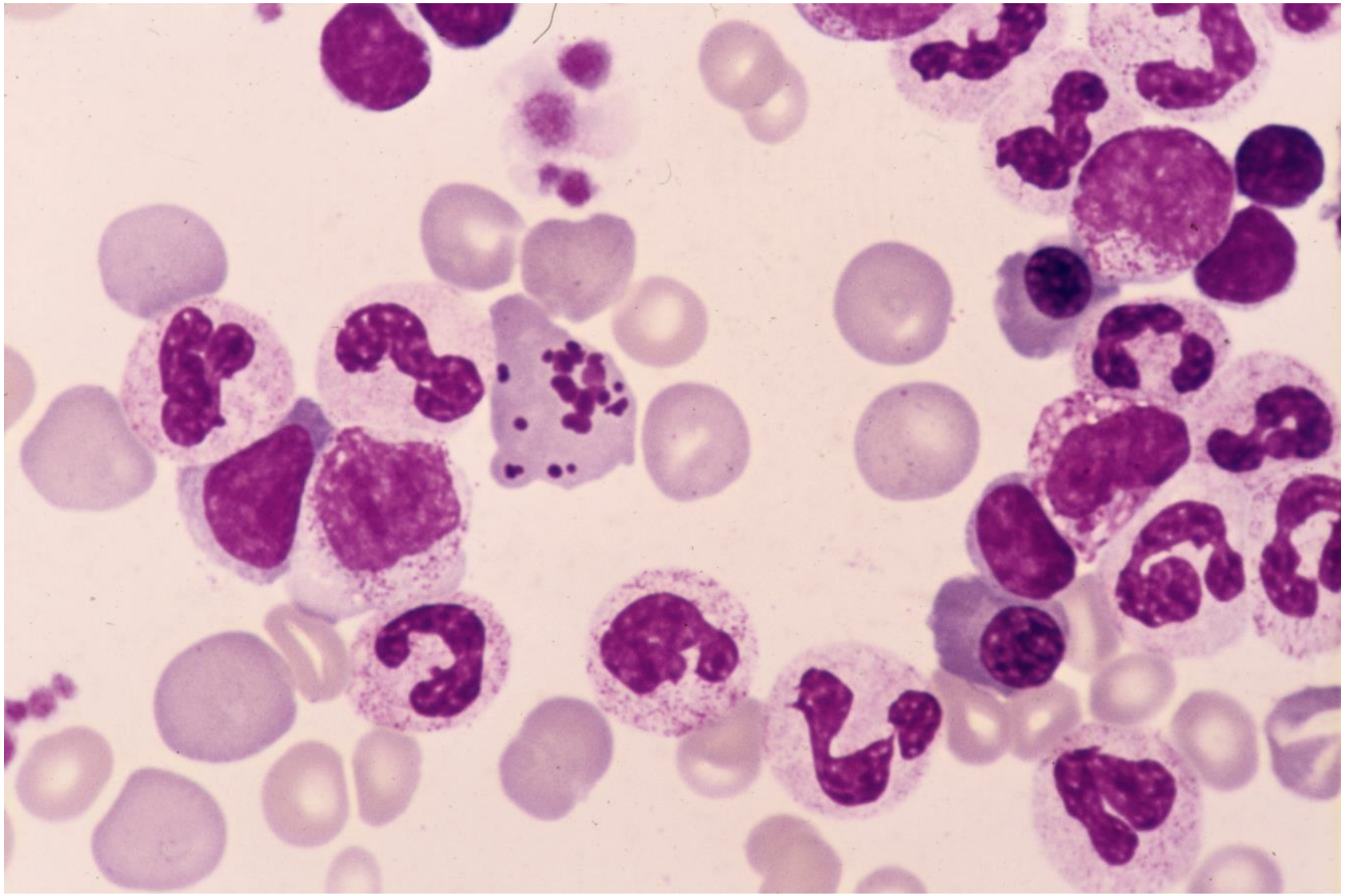


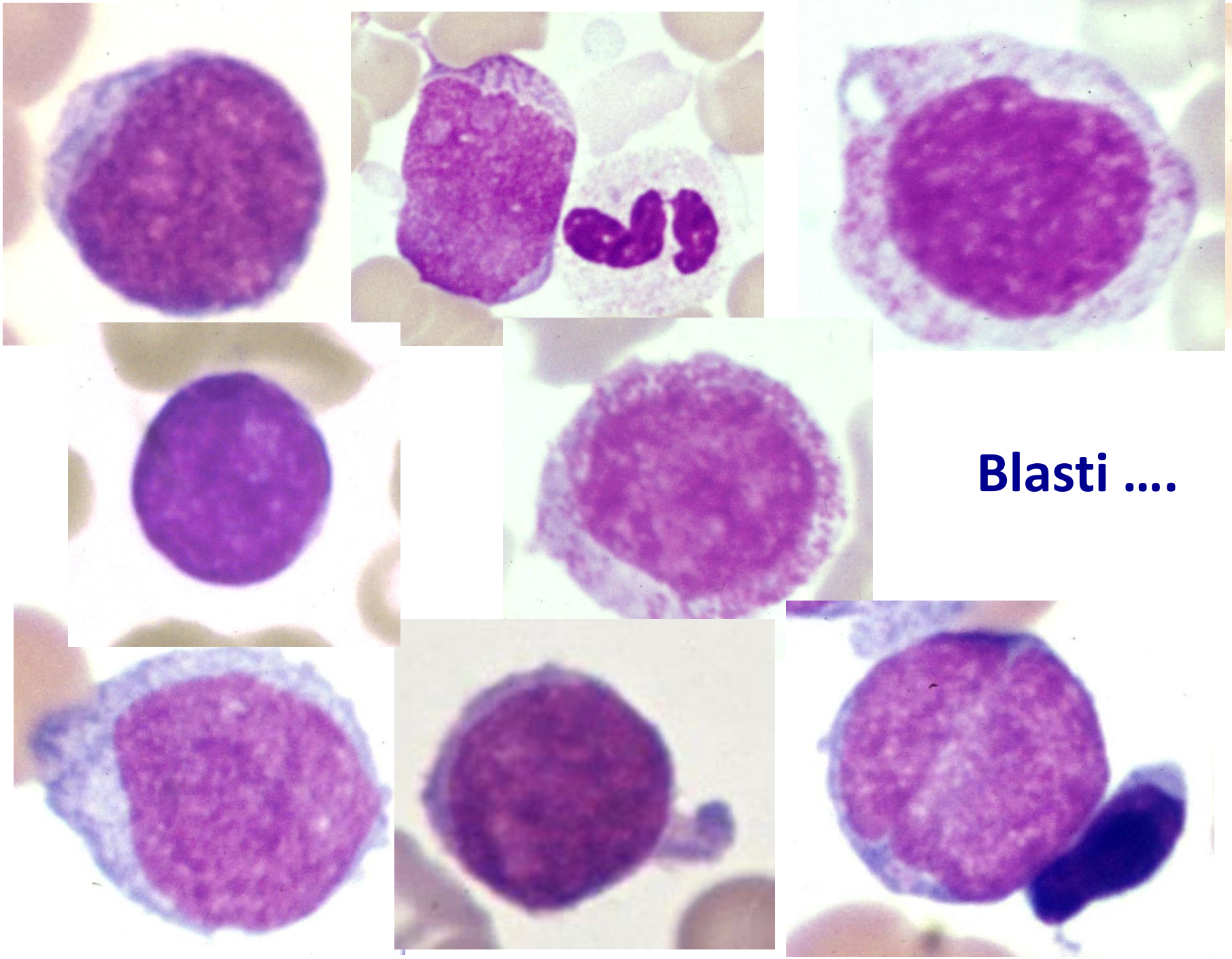
Citopenia Refrattaria con displasia multilineare

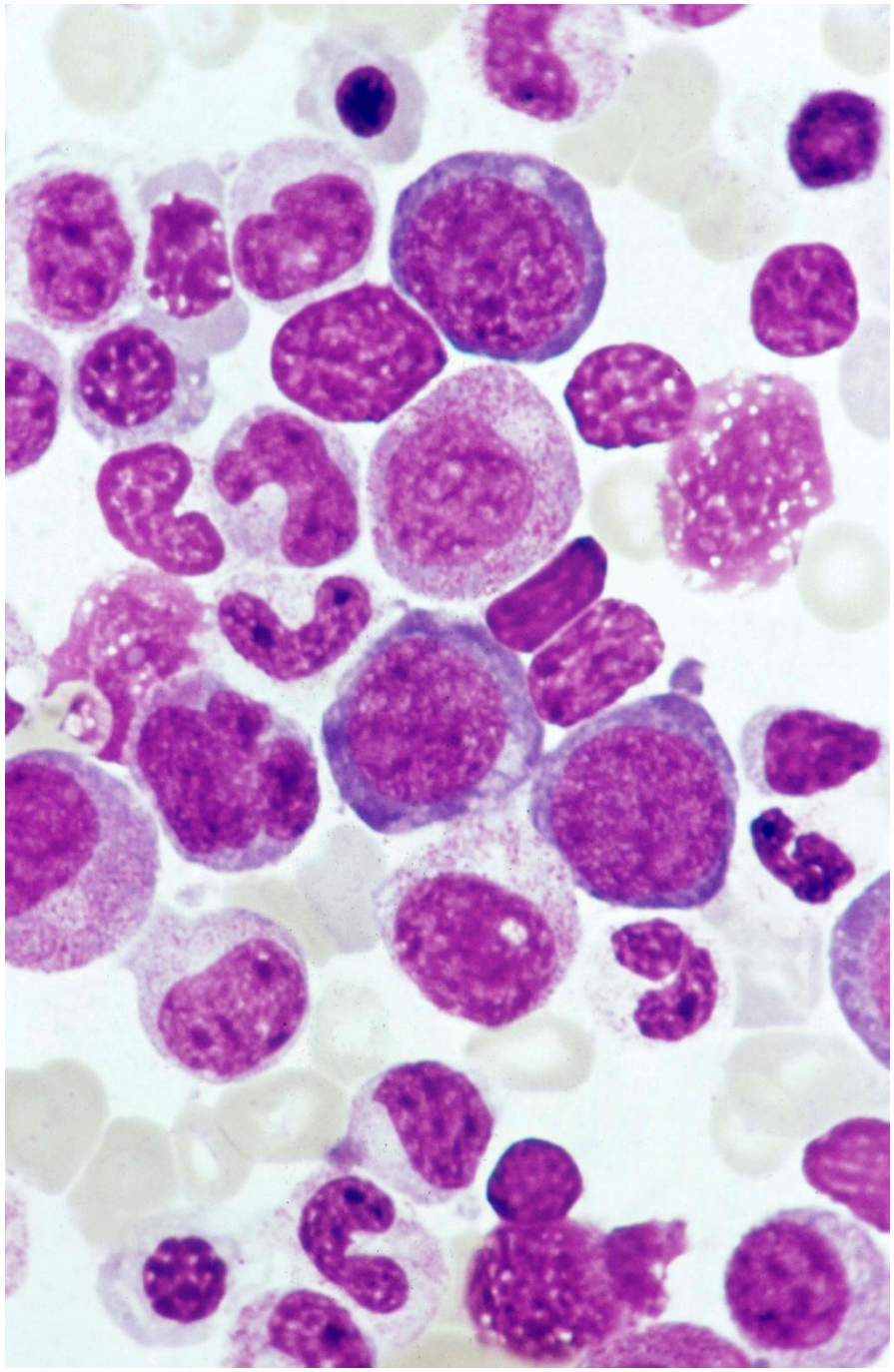
MO

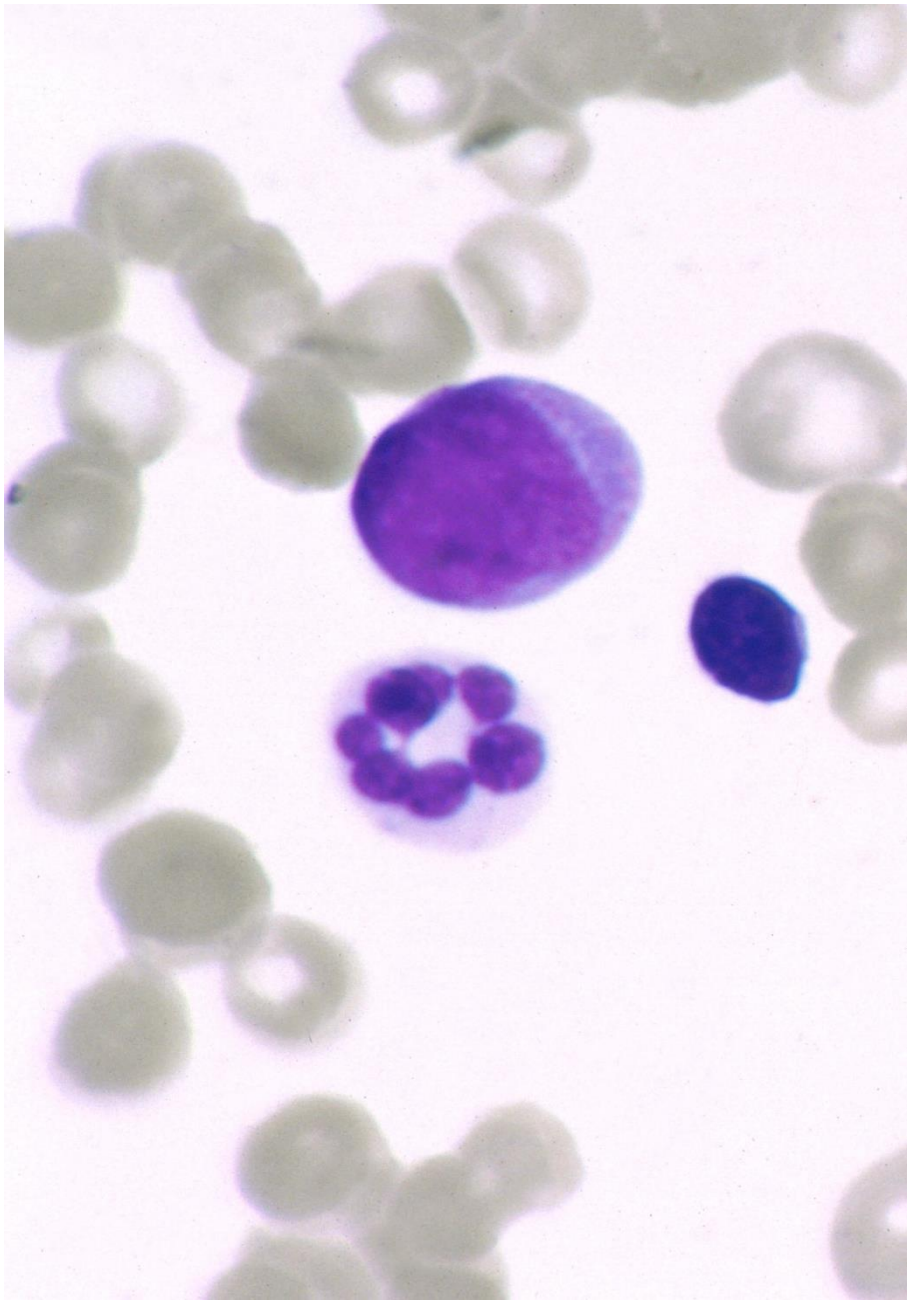
- ✓Displasia >10% delle cellule in 2 o più linee mieloidi
- ✓Neutrofili ipogranulati e/o con nuclei iposegmentati (nuclei pseudo Pelger-Huet)
- ✓In alcuni casi marcata iperplasia e displasia eritroide
- ✓Sideroblasti ad anello <15% dei precursori eritroidi
- ✓Se sideroblasti ad anello >15%: diagnosi di RCMD-RS
- ✓Micromegacariociti o megacariociti con nuclei ipolobulati
- ✓Mieloblasti <5%

Anomalie citogenetiche (50% dei casi): +8, -5, del(5q), -7, del(7q), del(20q), cariotipi complessi




Blasti ….





Anemia Refrattaria con eccesso di blasti

Pe

- ✓Frequente displasia trilineare
- ✓Anisopoichilocitosi con macrociti
- ✓Neutrofili ipogranulati e con nuclei iposegmentati (nuclei pseudo Pelger-Huet)
- ✓Blasti <5% (AREB-1)
  5-19% (AREB-2)

Anemia Refrattaria con eccesso di blasti

MO

✓Iperplasia neutrofila con vario grado di displasia: disgranulopoiesi, nuclei pseudo Pelger-Huet, nuclei ipersegmentati

✓Diseritropoiesi eritroide con nuclei multilobati e magaloblastoidi

✓Displasia megacariocitaria con micromegacariociti ipolobulati, non lobulati o con nuclei multipli separati

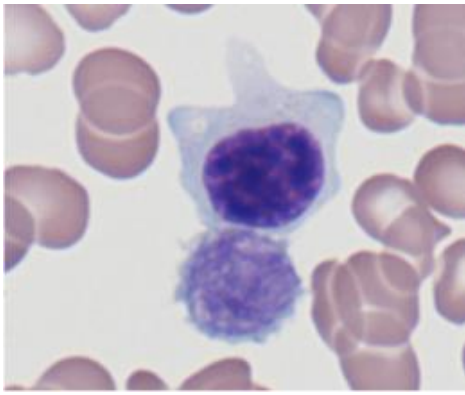
✓Corpi di Auer (AREB-2)

✓BOM: ipercellularità frequente, ipocellularità nel 10-15% dei casi
Anomala localizzazione dei precursori immaturi (ALIP)

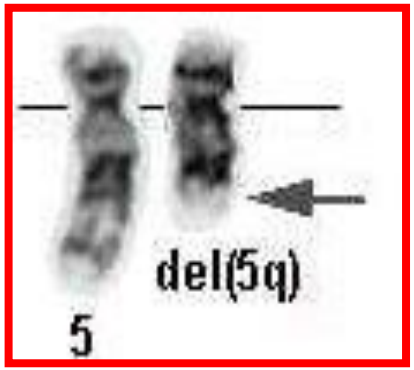
✓Mieloblasti 5-9% (AREB-1)
10-19% (AREB-2)

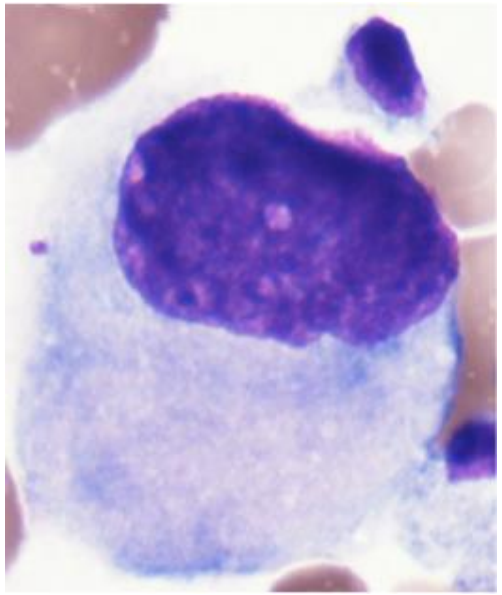
Anomalie citogenetiche (30-50% dei casi): +8, -5, del(5q), -7, del(7q), del(20q), cariotipi complessi

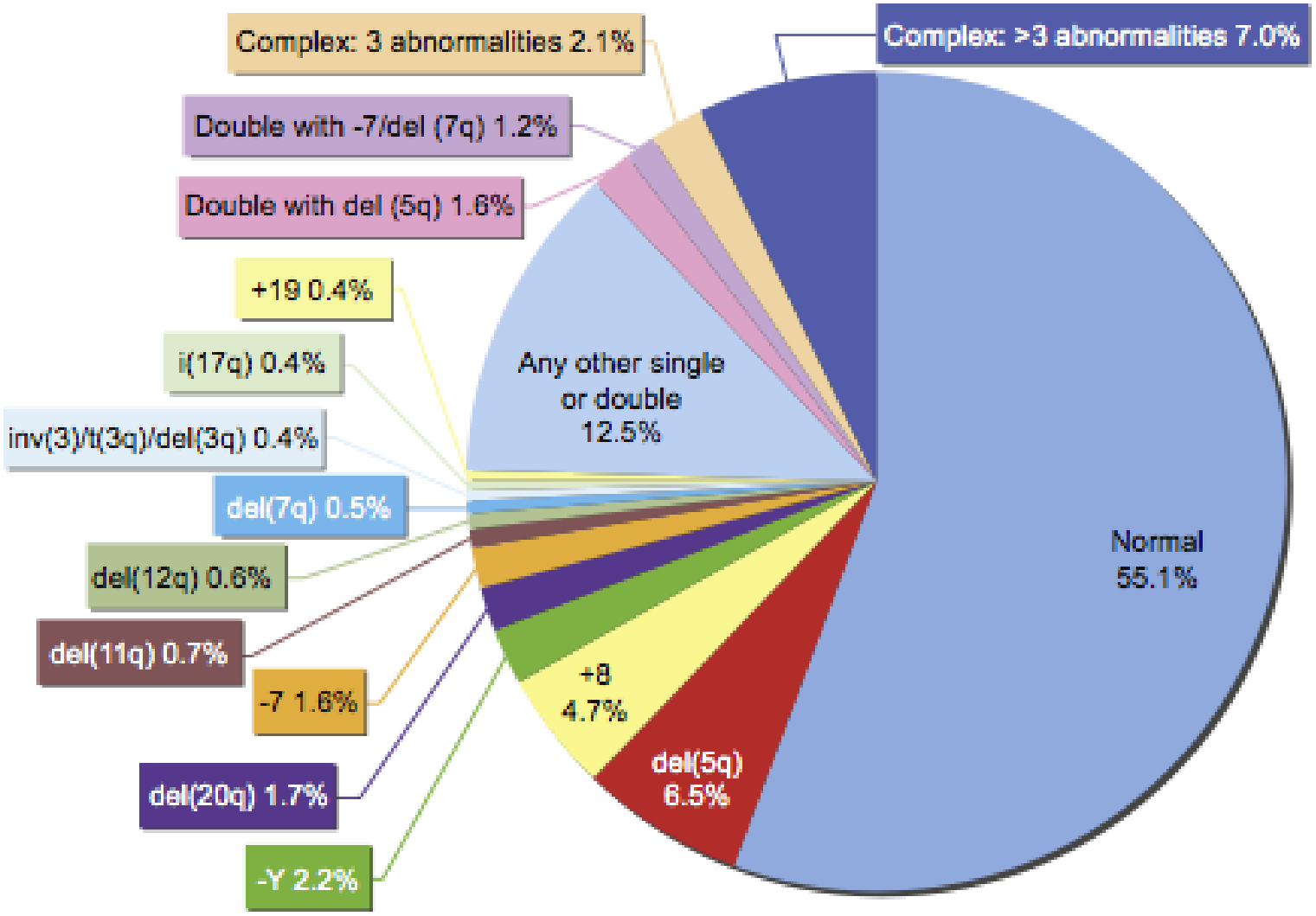
5q- Syndrome



- **5q- as the sole anomaly**
- M/F 1:4
- Macrocytic anemia
- Mononuclear Mk-cytes
- Reduced BFU-E growth, normal CFU-GM growth
- Erythroid hypoplasia
- **Favourable clinical course**
- **Leukemic transformation rare**
- Transfusion dependence = negative impact
- **Response to lenalidomide**







Schanz te al JCO 2012

Sindromi mielodisplastiche inclassificabili

Pe

✓ Blasti assenti

✓Neutropenia o trombocitopenia

MO

✓Displasia marcata della linea neutrofila e megacariocitaria

✓BOM: ipercellularità frequente, normocellularità o ipocellularità rare

✓Blasti assenti

Anomalie citogenetiche:Cariotipo spesso normale o anomalie simili agli altri sottotipi di MDS

Oggi la dx di MDS deve essere effettuata secondo i criteri WHO