FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE



CONVEGNO FISiM

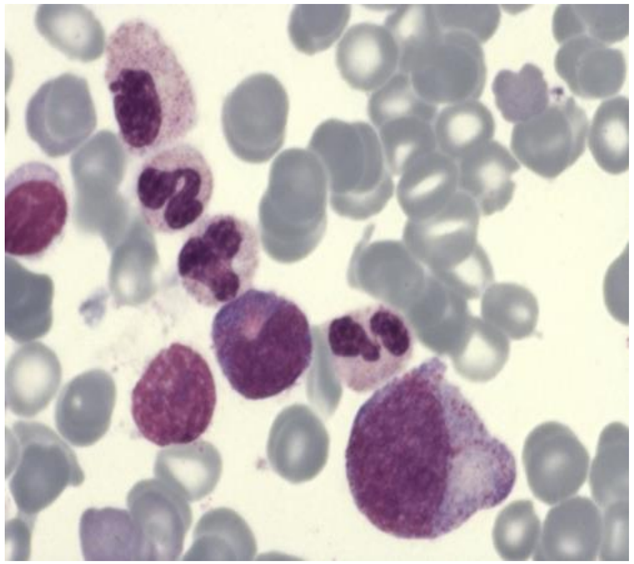
Firenze, CSF Montedomini
"Il Fuligno"
23-24 ottobre 2026

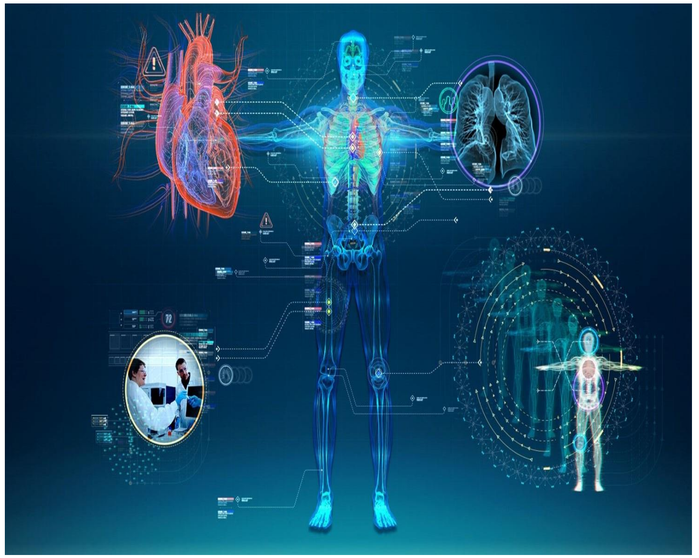
L'importanza della morfologia nelle MDS: discussione di casi clinici

Susanna Fenu
Roma

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Jazz							







HA ANCORA UN RUOLO FONDAMENTALE NELLA DIAGNOSTICA DELLE EMOPATIE ?

E' UNA DISCIPLINA ANTIQUATA, IMMODIFICATA, IMMODIFICABILE ?

Elizabeth L. Courville, MD, Technology Spotlight
Digital Microscopy and Artificial Intelligence in Bone Marrow Evaluation:

- We strongly recommend that operators should be trained on this “new morphology” just as they are trained in the interpretation of cytogramsfrom automated cell counters.

(ICSH2 019)

- Inaccurate identification of abnormal cells remains still challenging, in spite of advancements in digital imaging and AI algorithms.
- Specifically, immature granulocytes, eosinophils, and basophils can be difficult to detect accurately using automated methods

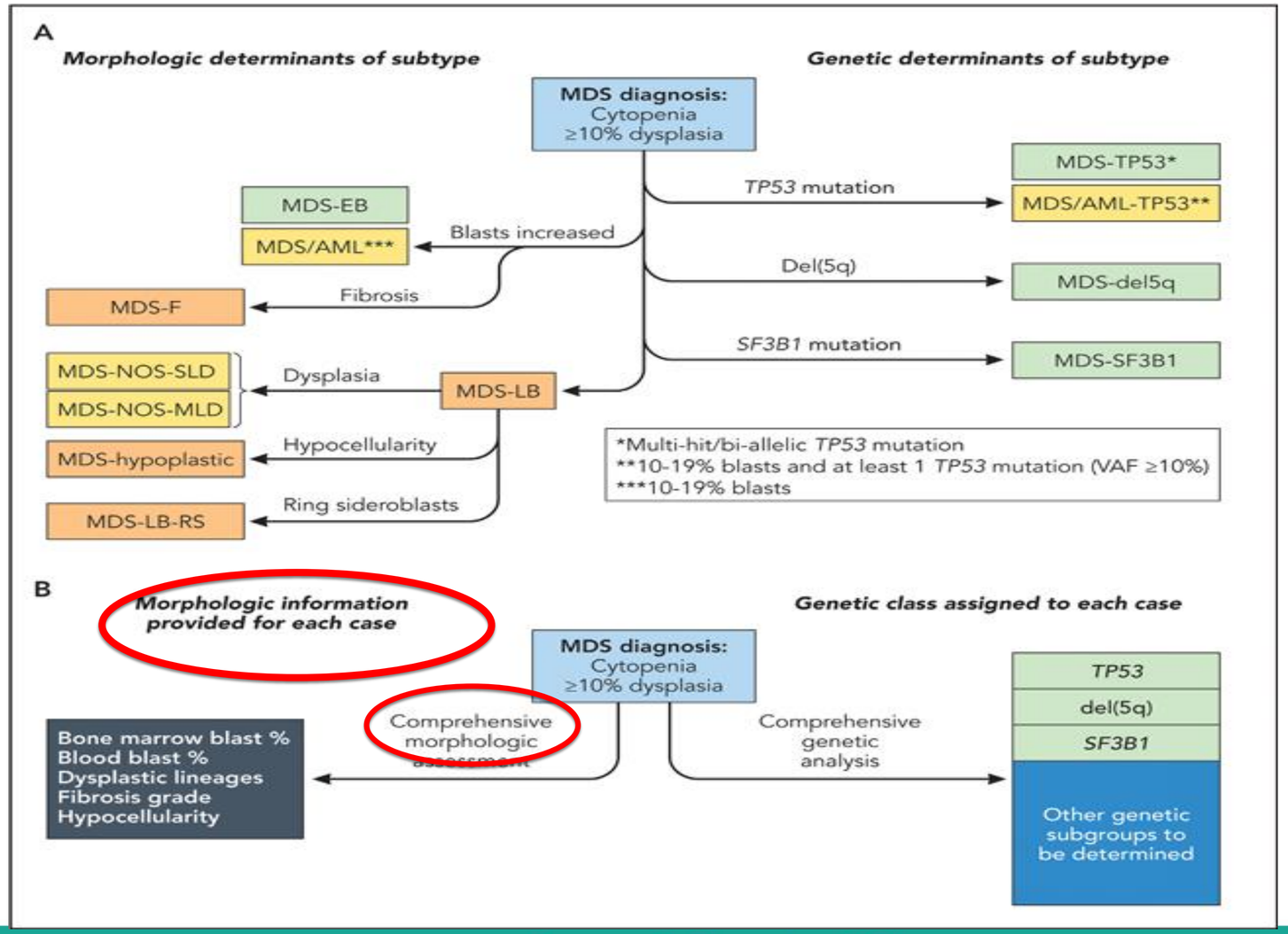
(H- Kim et all, Diagnostics 2025)

MYELODYSPLASTIC SYNDROMES IN THE AGE OF GENOMIC MEDICINE

Diagnosis and classification of myelodysplastic syndromes

Robert P. Hasserjian,[1] Ulrich Germing,[2] and Luca Malcovati[3,4]

[1]Department of Pathology, Massachusetts General Hospital, Boston, MA; [2]Department of Hematology, Oncology, and Clinical Immunology, Heinrich-Heine University, Dusseldorf, Germany; [3]Department of Molecular Medicine, University of Pavia, Pavia, Italy; and [4]Department of Hematology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy

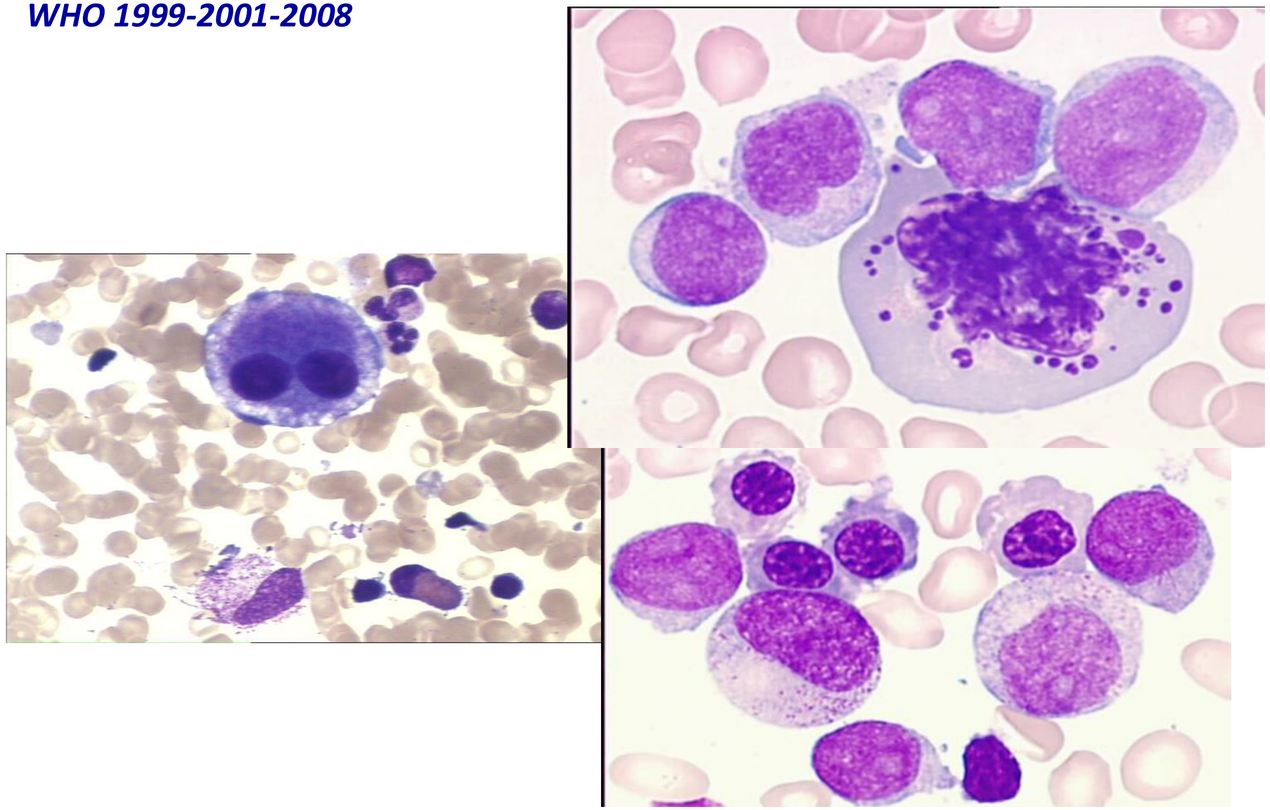


MDS: CRITERI DIAGNOSTICI (displasia per filiera >10%)

Briito-Babapulle F.,Catovsky D.,Galton D.,Br.j.Haemat1987;66:445-454
Goasguen,Matsuo,Benett: Leukemia 6(6) 1992,520-525
WHO 1999-2001-2008

Sangue midollare e Periferico

- **Diseritropoiesi**
- **Disgranulopoiesi**
- **Dismegacariopoiesi**

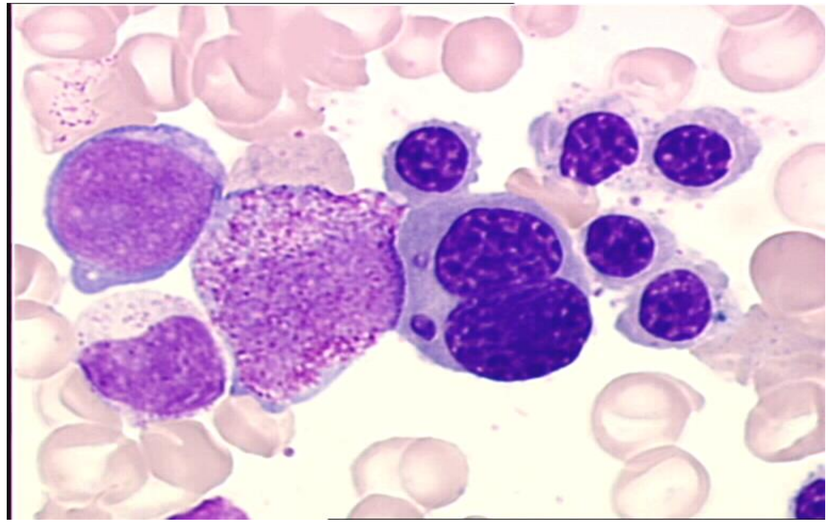


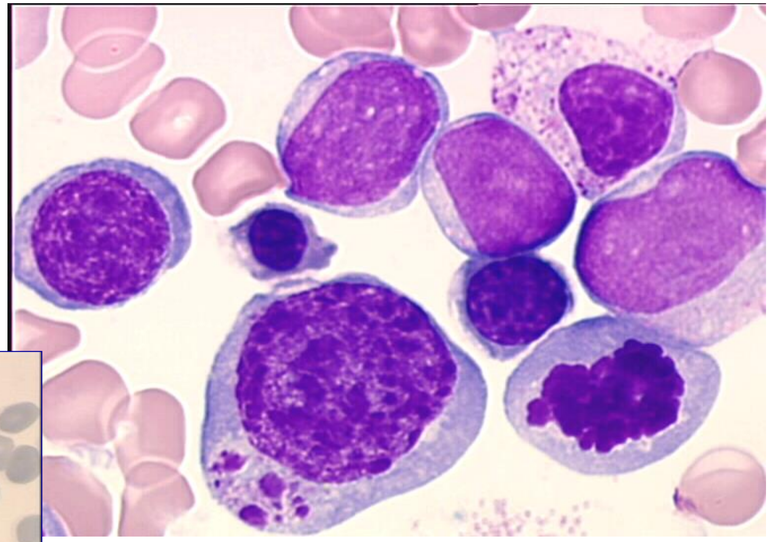
Percentuale di Blasti (AC)):

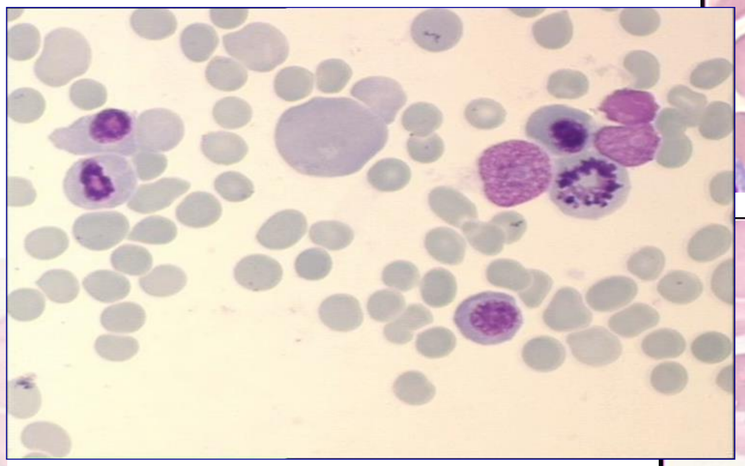
- **Mieloblasti agranulati (Tipo I)**
- **Mieloblasti granulati (TipoII)**
- **Blast equivalents (Promonociti ,micromegacarioblasti)**

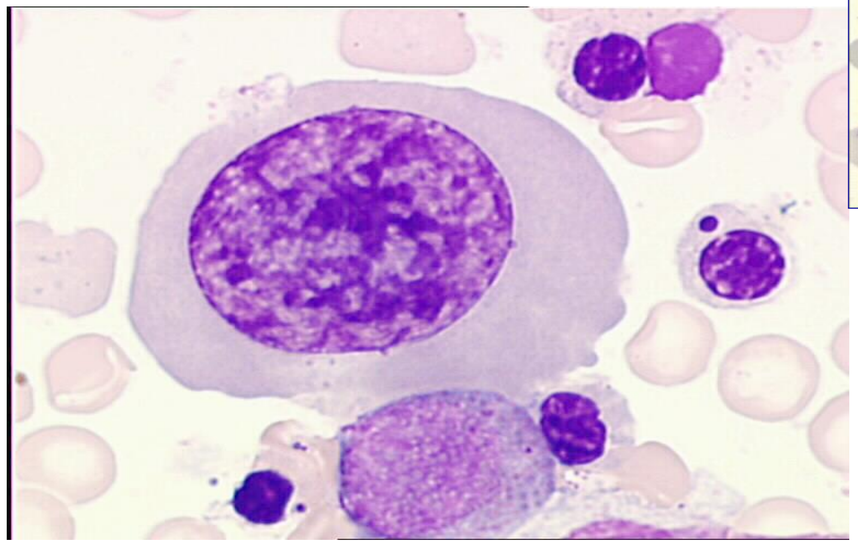
Morphology remains the cornerstone of diagnosis:Well-stained blood and BM smears; well-processed BM biopsies

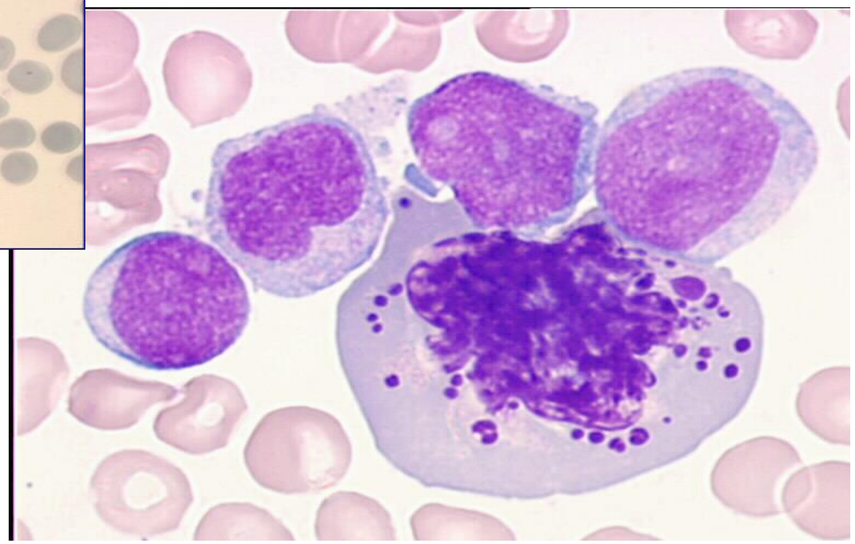
ERITRODISPLASIA



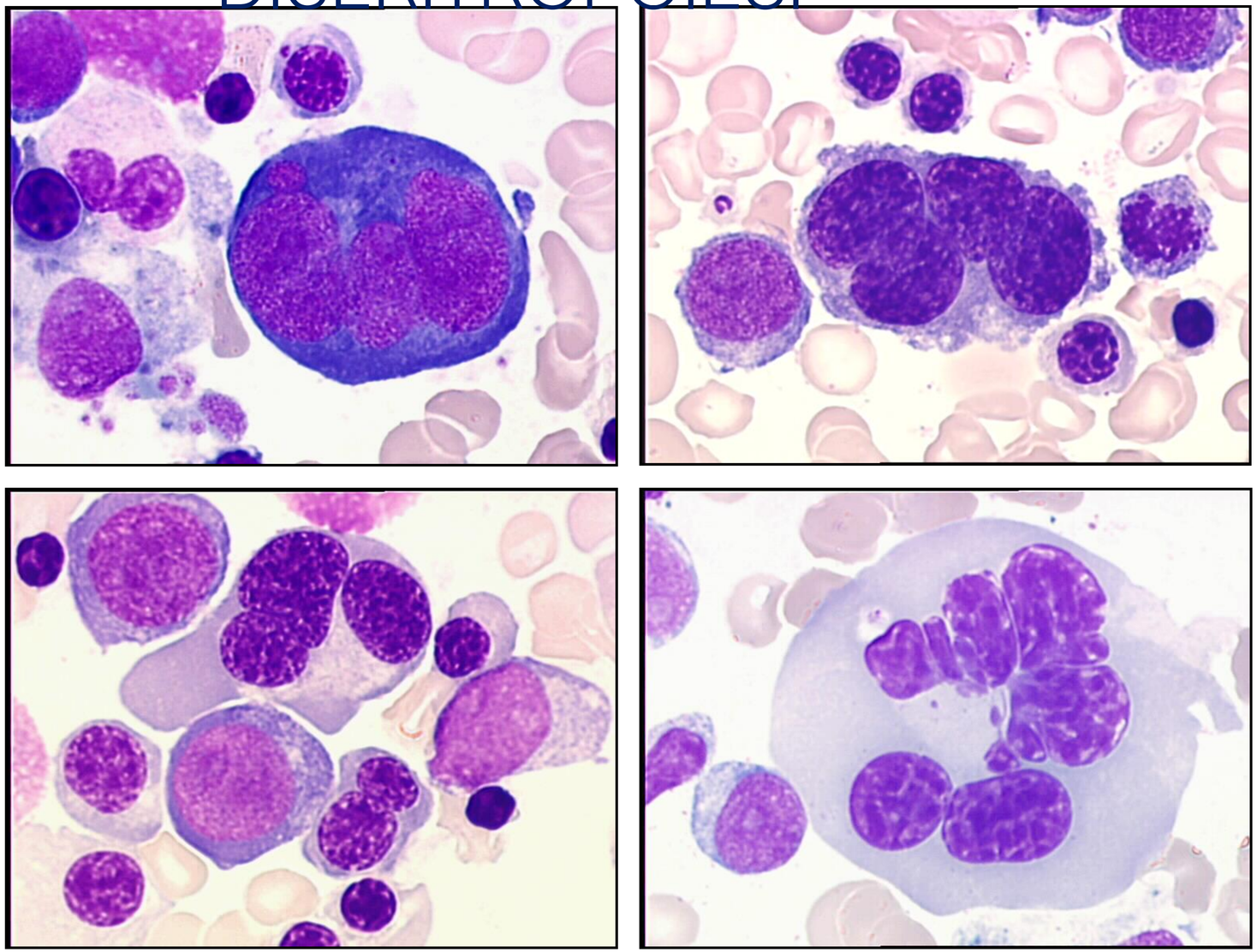






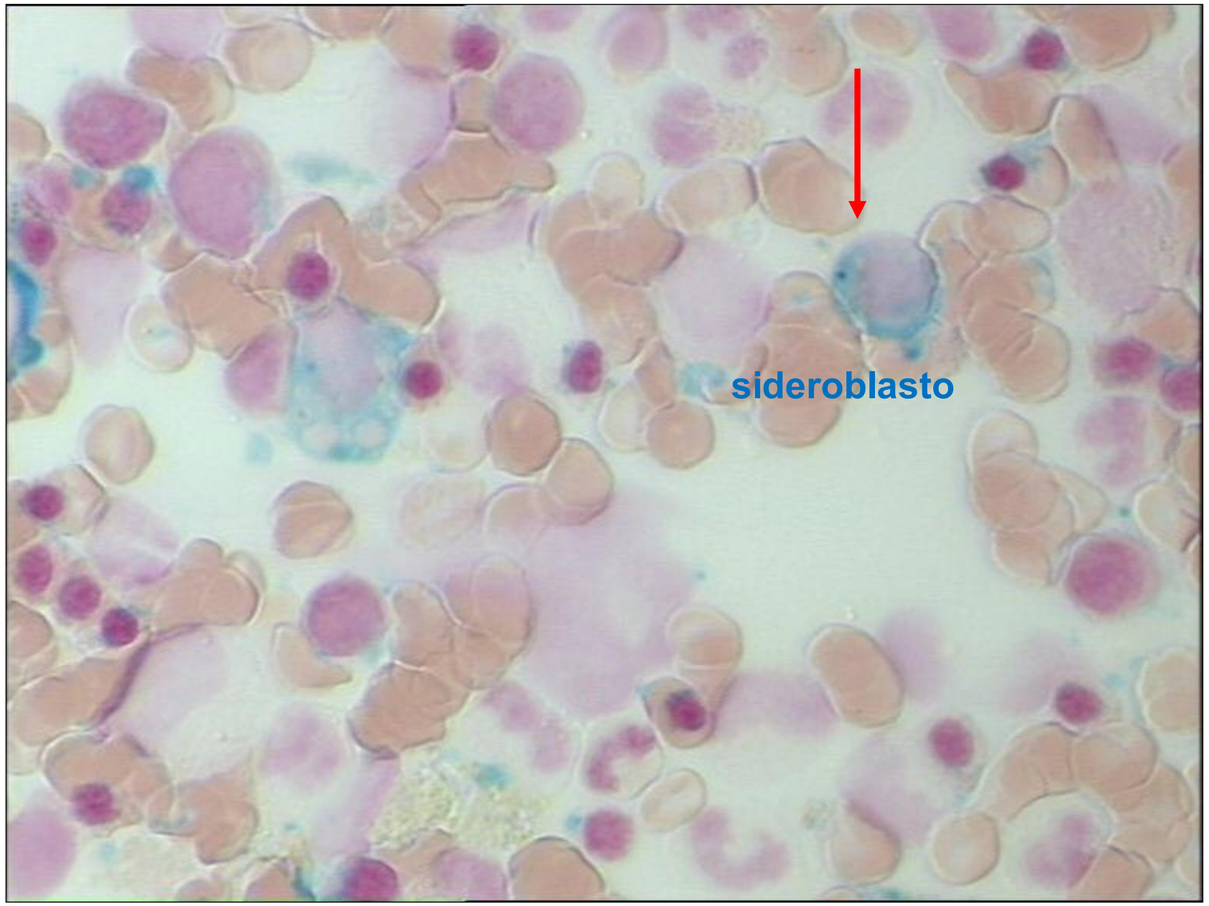


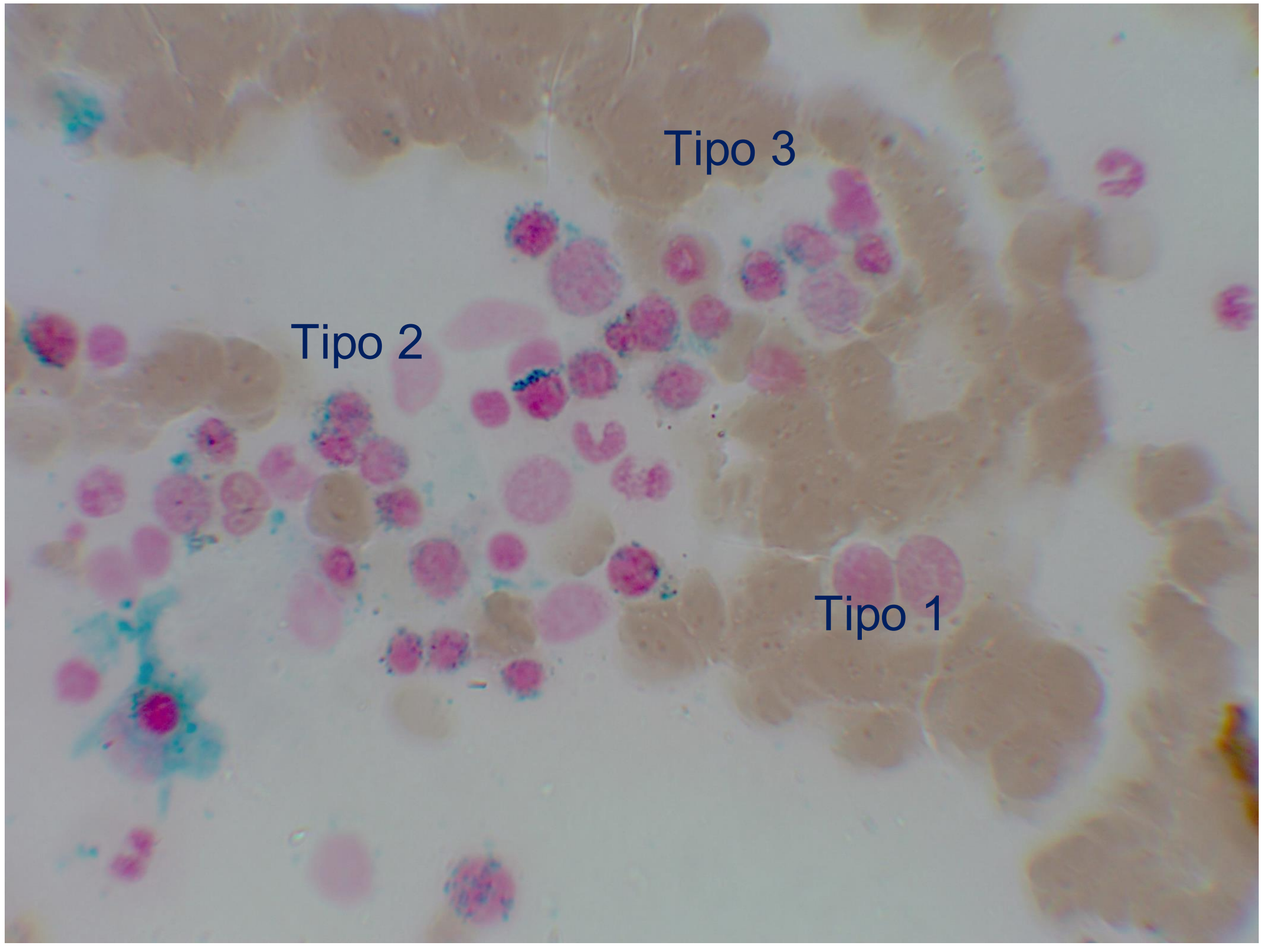
DISERITROPOIESI

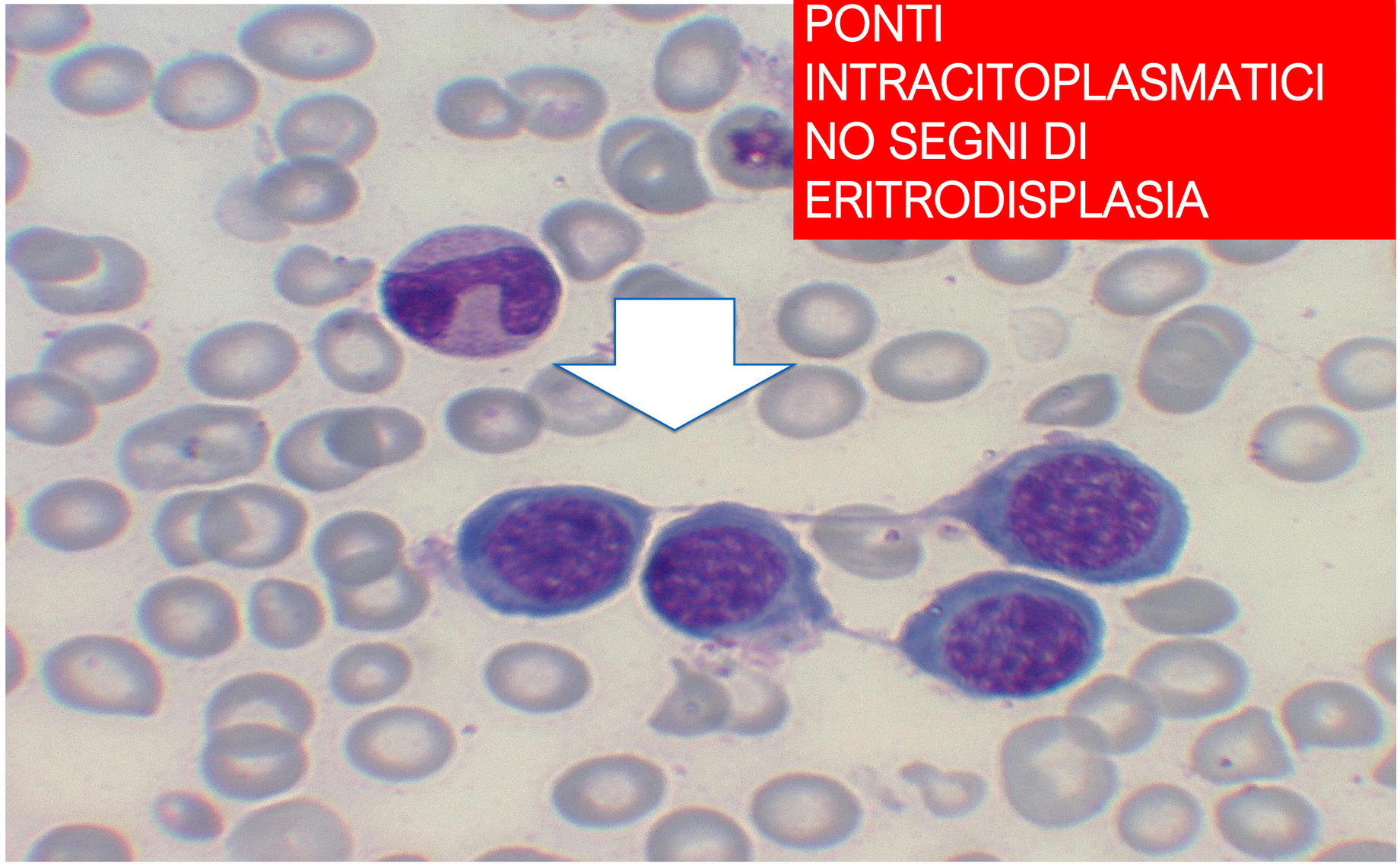


AM MGG 1000x

Courtesy Prof Daniel


sideroblasto

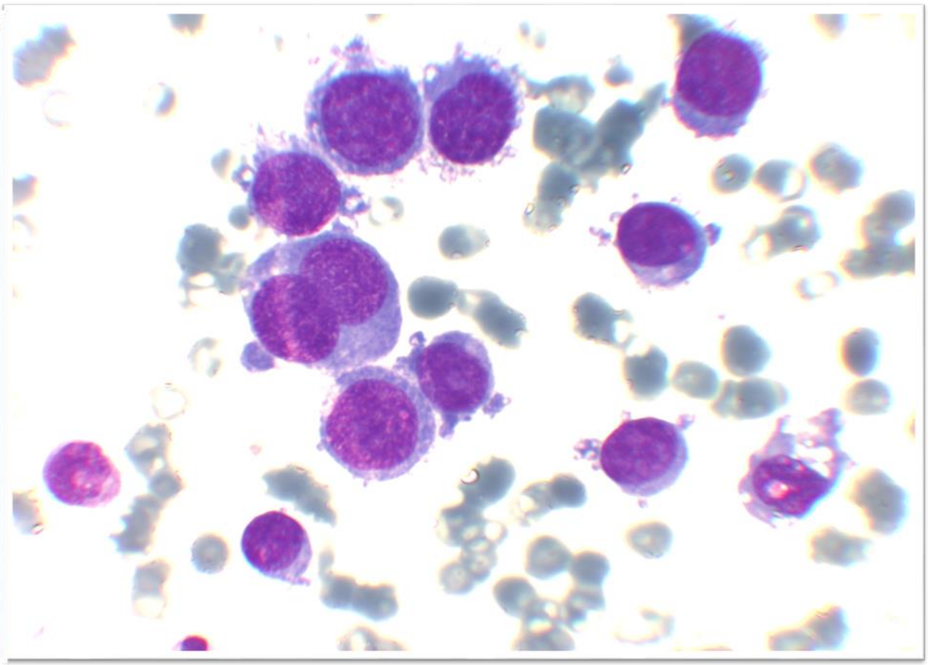

Tipo 3
Tipo 2
Tipo 1


PONTI
INTRACITOPLASMATICI
NO SEGNI DI
ERITRODISPLASIA

Diagnosi
Precursori eritroidi >80% di cui > 30% sono PROERITROBLASTI
Morfologia :
Sangue periferico presenza di precursori ertroidi
Aspirato Midollare media grossa taglia
Nucleo : rotondo fine cromatina dispersa 3 nucleoli spesso binuclati
Citoplasma intesamente basofilo con vacuolizzazioni
Citochimica : SBB / MPO neg
PAS positivo tipo granulare

Se presente TP53 diagnosi "AML with TP53 mutation
Diagnosi Differenziale
AML –MR Megaloblastosi da deficit B12

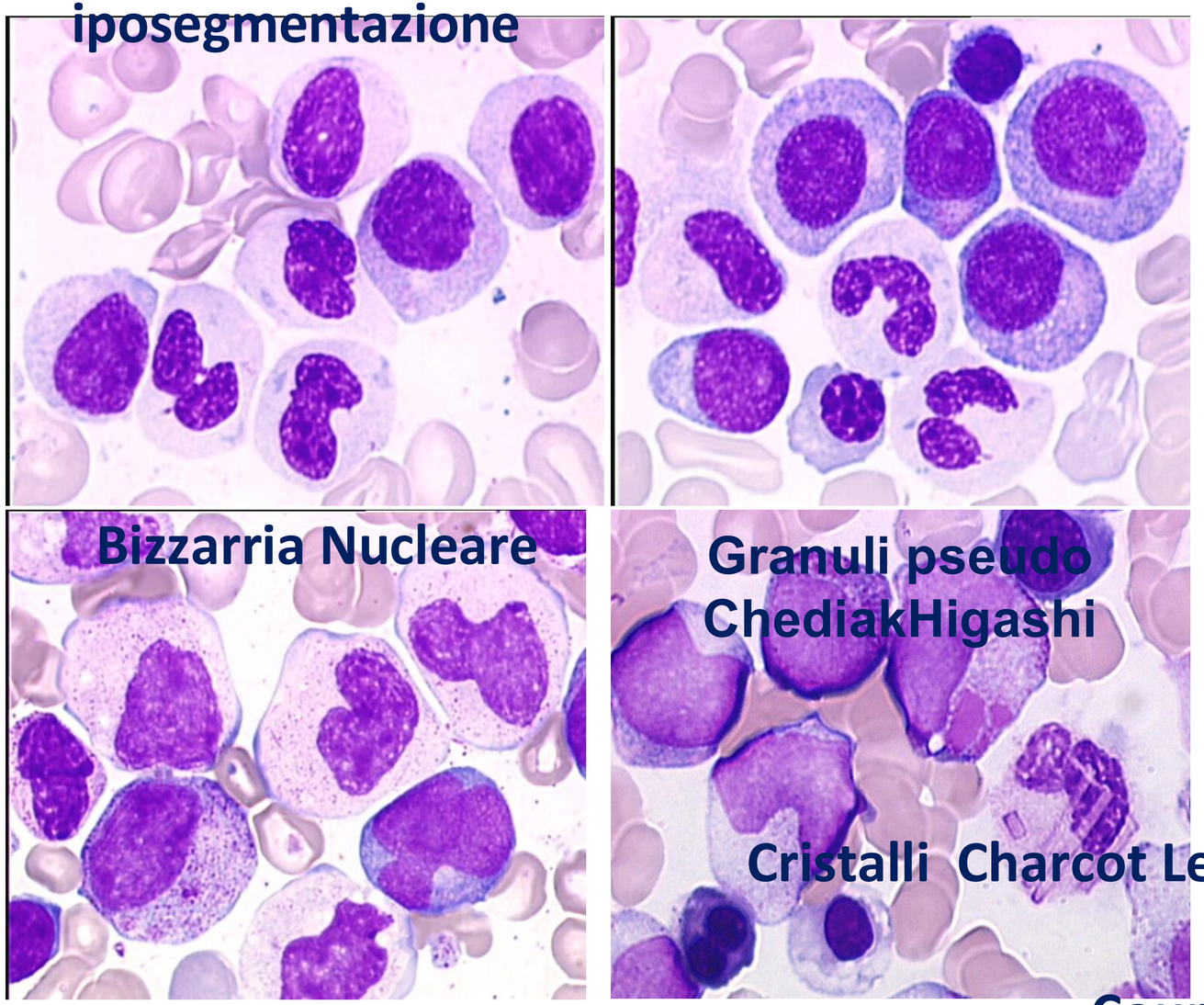




Leucemia eritroide Acuta /PEL

Acute erythroid leukaemia (AEL) (previously pure erythroid leukaemia, an acceptable related term in this edition) is a distinct AML type characterized by neoplastic proliferation of erythroid cells with features of maturation arrest and high prevalence of biallelic TP53 alterations. Diagnostic criteria include erythroid predominance, usually ≥80% of bone marrow elements, of which ≥30% are proerythroblasts (or pronormoblasts .WHO 2022

DISGRANULOPOIESI



Courtesy of prof Daniel

AM MGG 1000x

How I investigate dysgranulopoiesis

Roshini Shekhar | Vishrut K. Srinivasan | Swati Pai

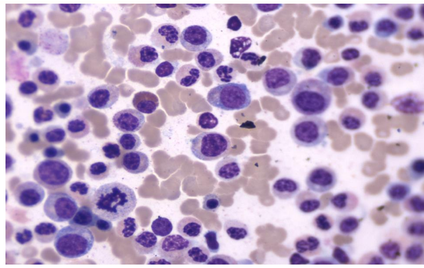
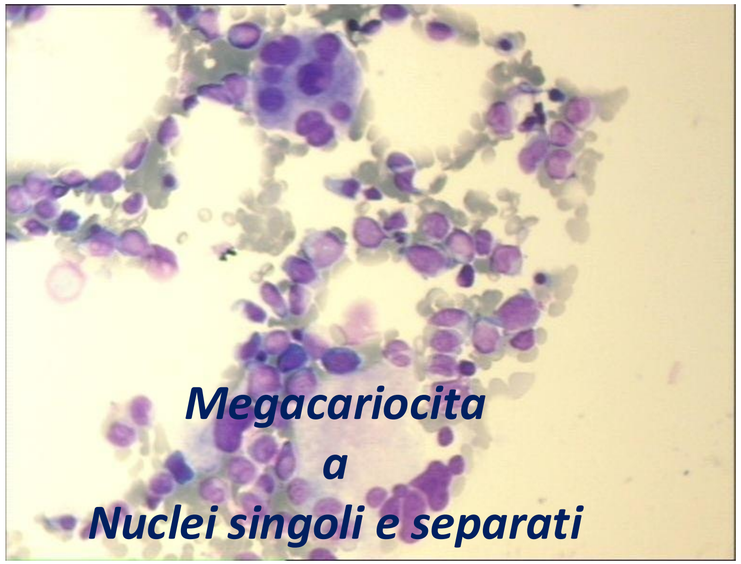


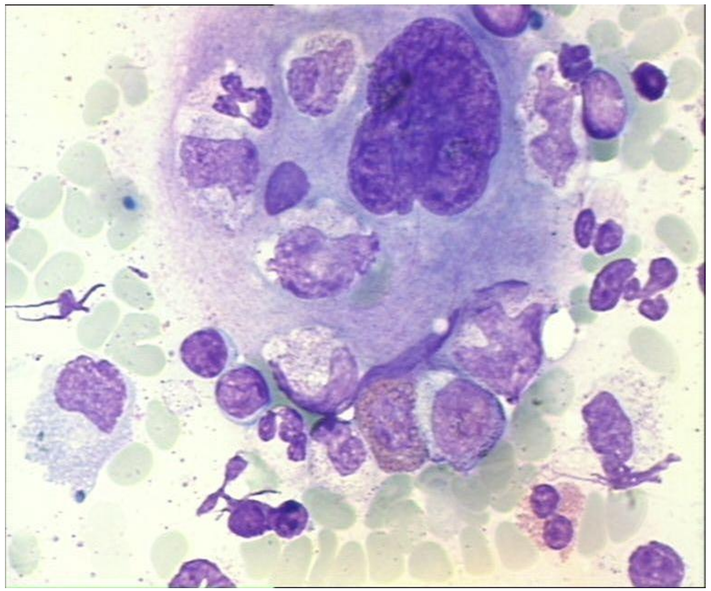
TABLE 1 Non-neoplastic causes of dysgranulopoiesis

Causes	Morphology findings	Recommended testing/workup
Nutritional		
Vitamin B12 deficiency	Nuclear-cytoplasmic dys-synchrony, hypersegmented granulocytes ("right shift"), giant myelocytes and metamyelocytes	Serum vitamin B12 levels, homocysteine and methylmalonic acid levels
Folic Acid deficiency		Red cell/serum folate levels, serum homocysteine
Copper deficiency	Dysplasia, cytoplasmic vacuolation of myeloid & erythoid precursors, ring sideroblasts	Serum copper levels
Infections		
Human immunodeficiency virus (HIV)	Megaloblastic changes, pseudo-Pelger-Huët anomaly, coarse granulation and degranulation of myeloid cells	HIV testing
Parvovirus	Myeloid hypogranulation, increase in myeloid blasts and monocytosis	Parvovirus IgG, IgM antibody levels, bone marrow smear examination for parvovirus inclusions and immunohistochemistry
Hepatitis C virus (HCV), Human herpesvirus-6 (HHV-6)	Dyserythropoiesis (more common), abnormal neutrophil lobation and/or cytoplasmic granulation	Testing for HCV, HHV-6 serological markers
Leishmaniasis	Multinucleation and pseudo-Pelger-Huët anomaly	rK39 antigen test, Antibody levels, bone marrow examination for L-D bodies
Autoimmune		
Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA)	Mild dysgranulopoiesis	Rheumatoid Factor, Autoimmune antibody profile including ANA, dsDNA, and anti-CCP
Drugs		
G-CSF/GM-CSF	Significant left-shifted myelopoiesis,marked hypergranularity, nuclear hyposegmentation and increase in blasts	History of G-CSF/GM-CSF treatment
Cotrimoxazole Tacrolimus Mycophenolate mofetil	Neutrophil hyposegmentation	History of drug therapy
Toxins		
Alcohol	Dysgranulopoiesis	History of alcohol use, smoking
Arsenic	Cytopenias and dyspoiesis	Serum arsenic levels
Smoking	Leucocytosis and right-shifted myelopoiesis	
Hereditary		
Hereditary autosomal dominant Pelger-Huët anomaly	Pelger-Huët anomaly and dysplasia	Peripheral blood smear examination of family members, Lamin B receptor (*LBR*) gene mutation testing
Pseudo-dysplasia		
EDTA effect, Poor preparation of slides	Hypogranulation of myeloid series	Examine slides as soon as possible; use of alternate anti-coagulants (heparin/citrate) Proper technique during slide preparation and staining

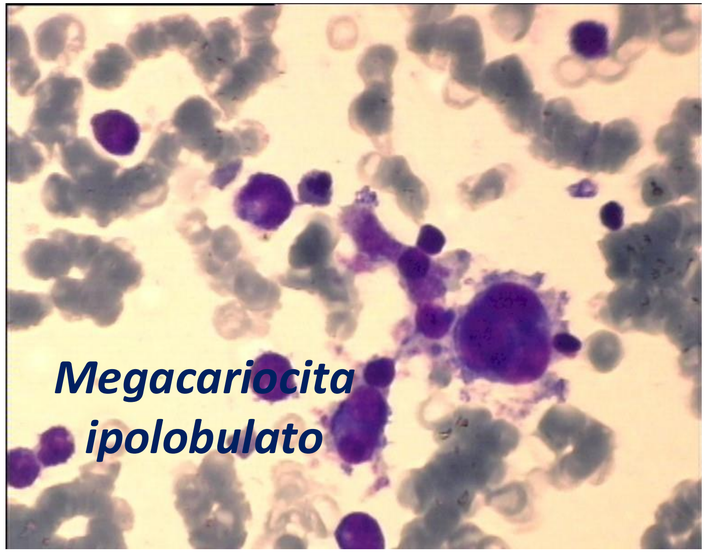
ISLH International Journal of Laboratory Hematology

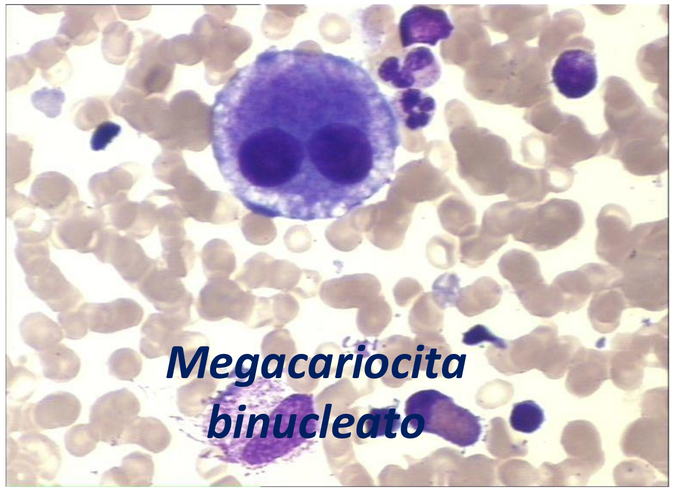
DISMEGACARIOPOIESI

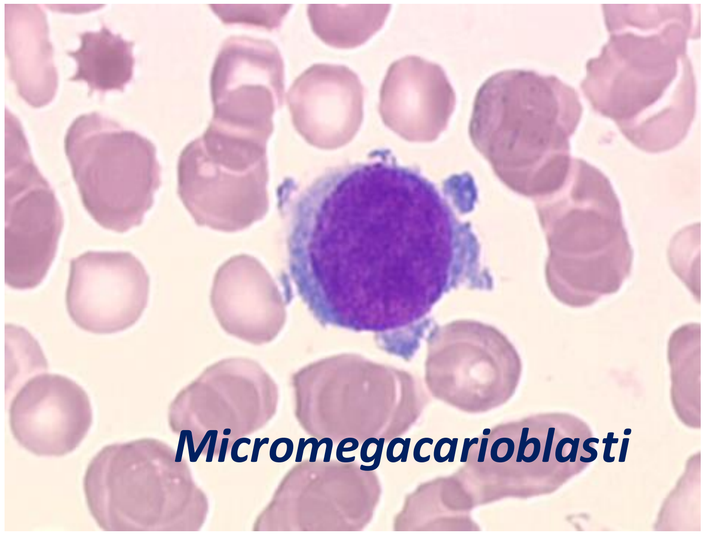




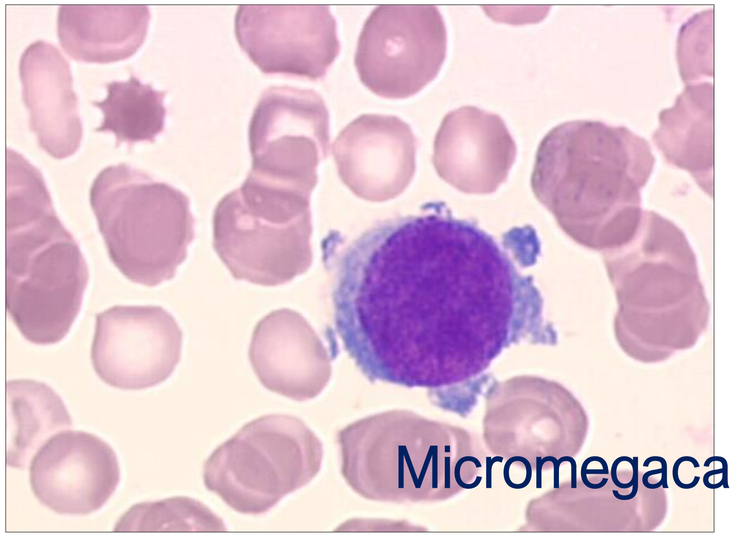
Emperipolesi non è segno patognomonico di MDS

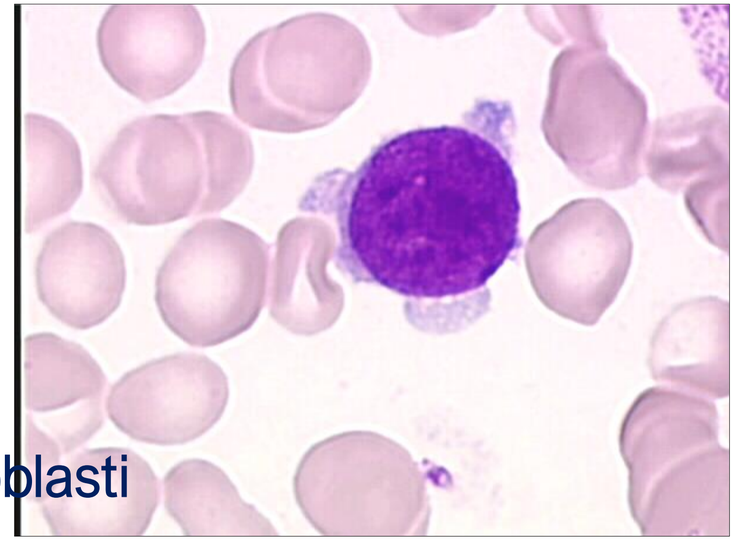




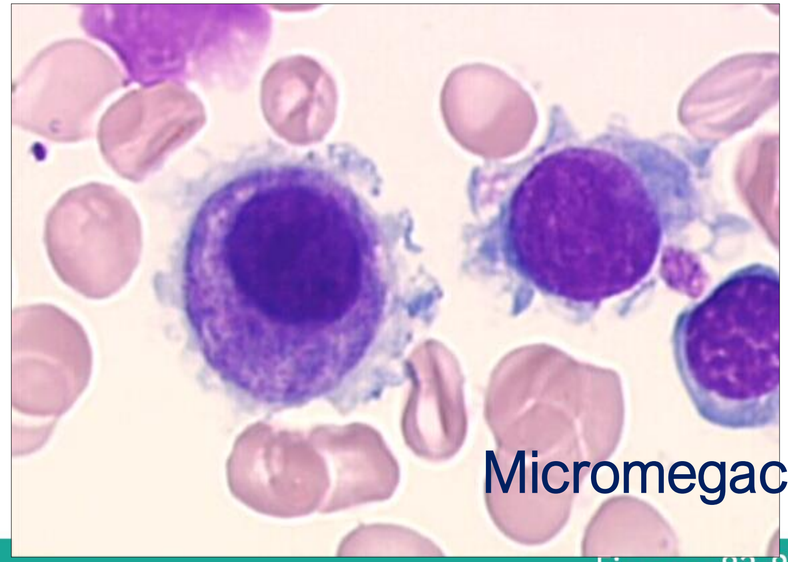


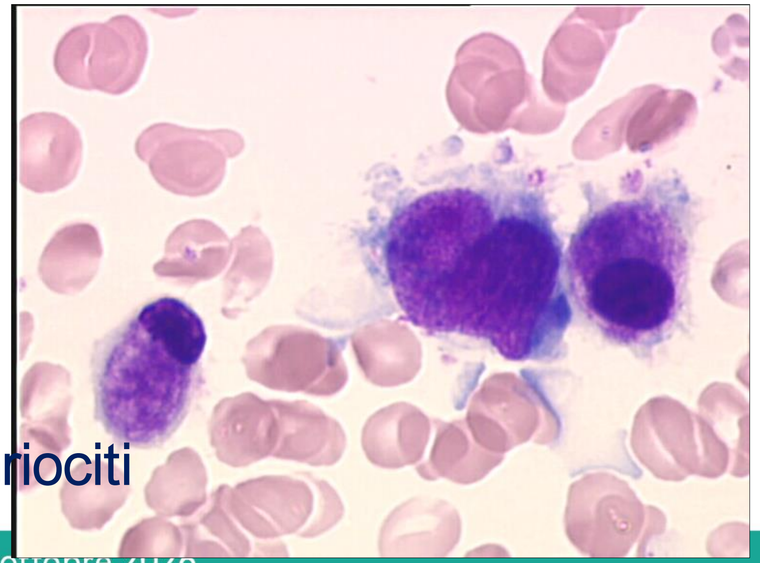
DISMEGACARIOPOIESI





Micromegacarioblasti

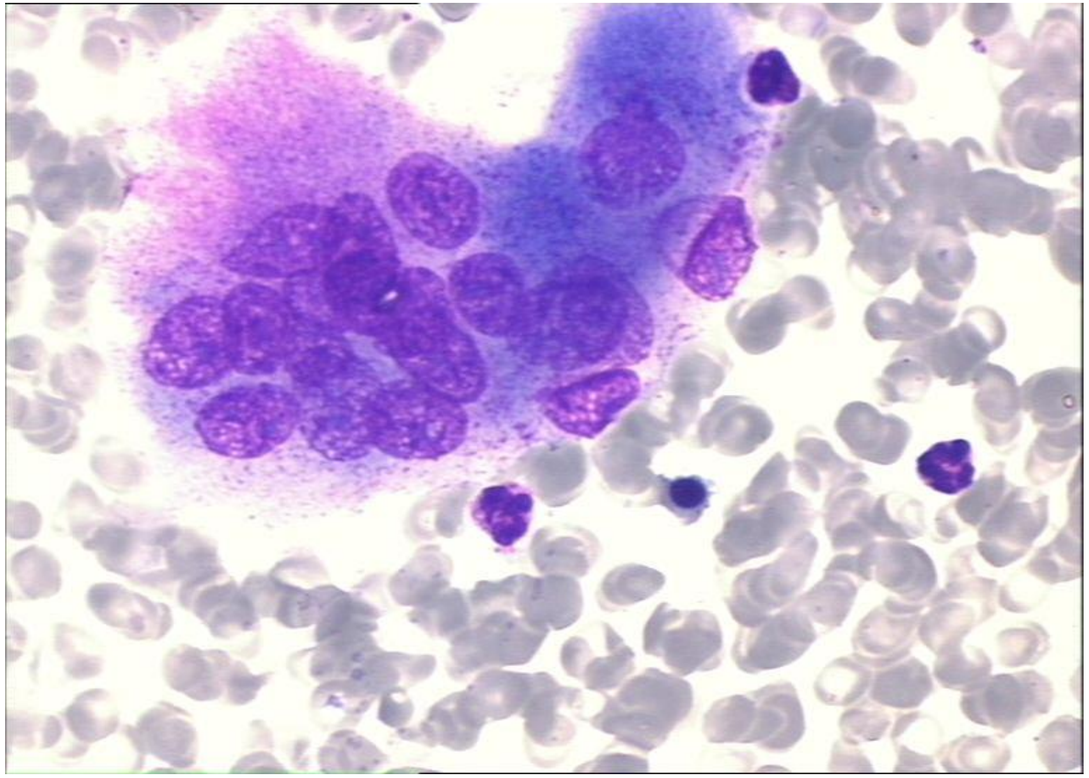




Micromegacariociti

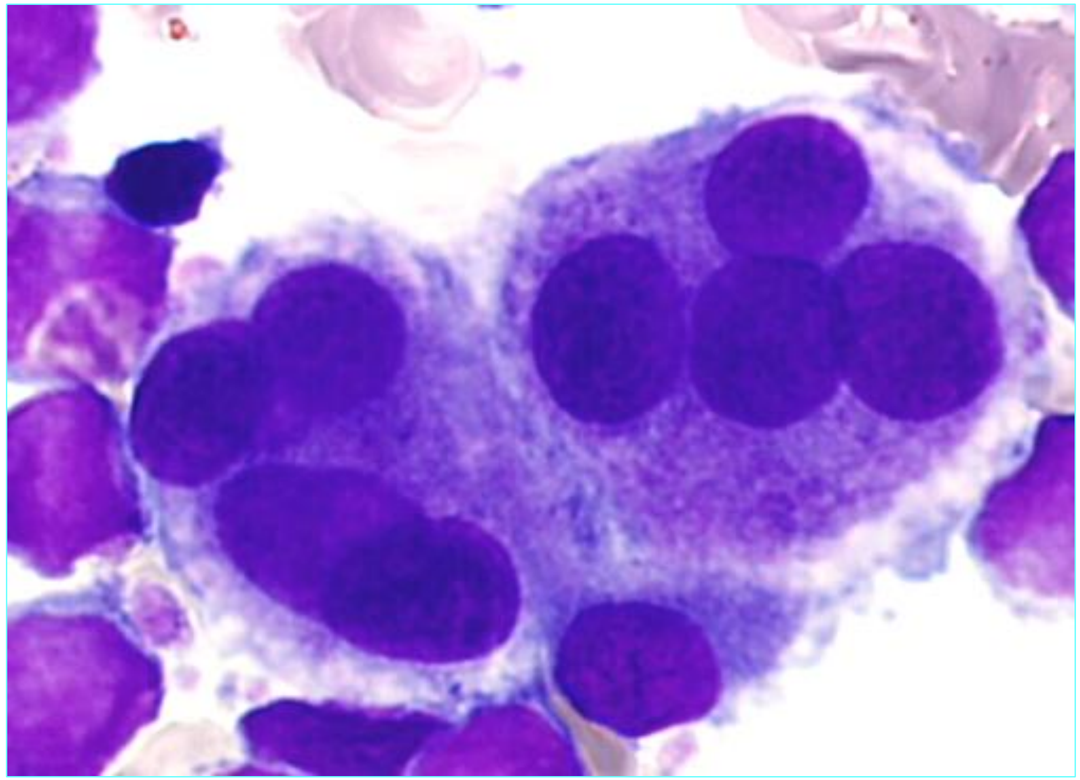
AM MGG 1000x

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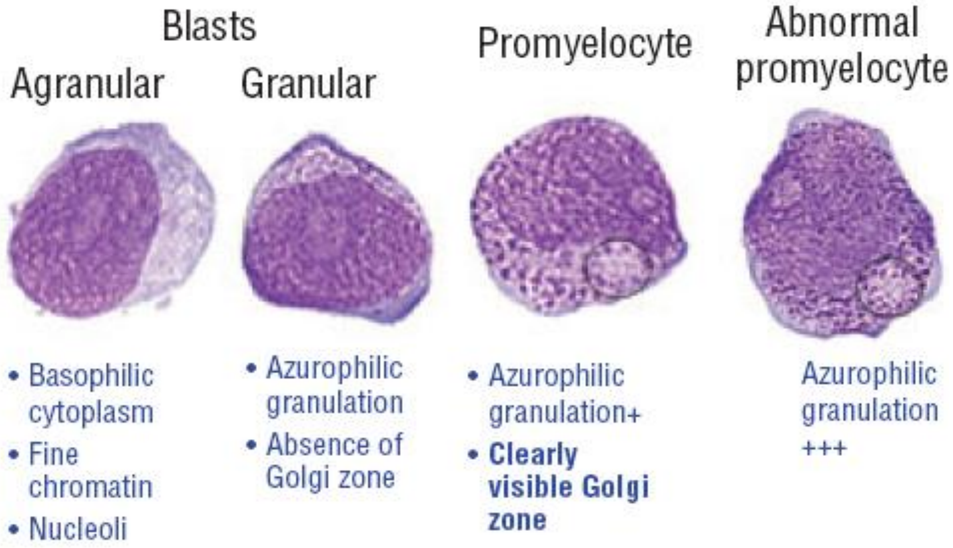
osteoclasto

AM MGG 1000x



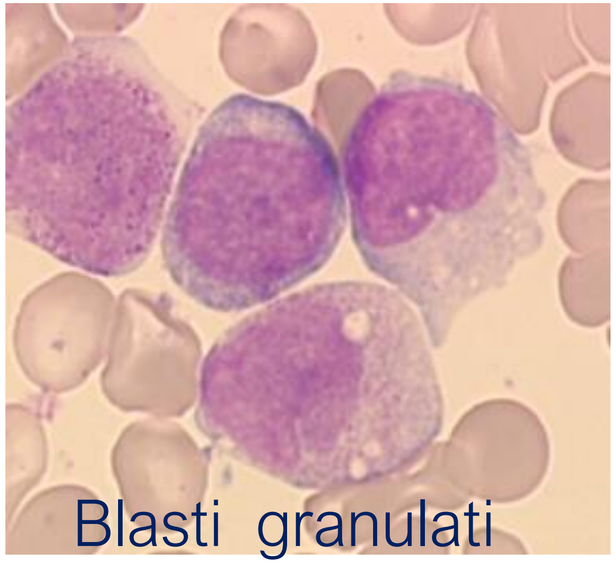
Megacariocita a nuclei multipli e separati

Diagnosis and classification of myelodysplastic syndrome: International Working Group on Morphology of myelodysplastic syndrome (IWGM-MDS) consensus proposals for the definition and enumeration of myeloblasts and ring sideroblasts

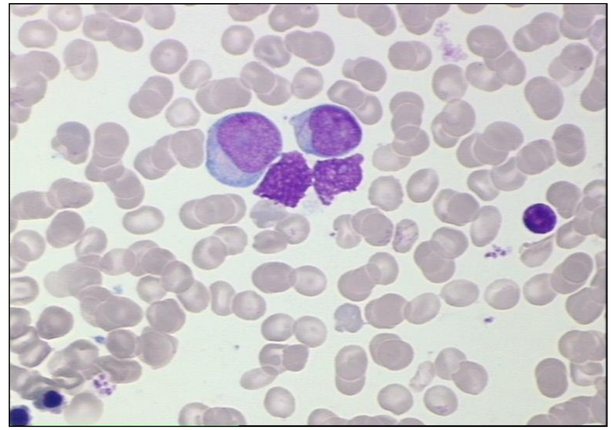


| 1714 | haematologica | 2008; 93(11)

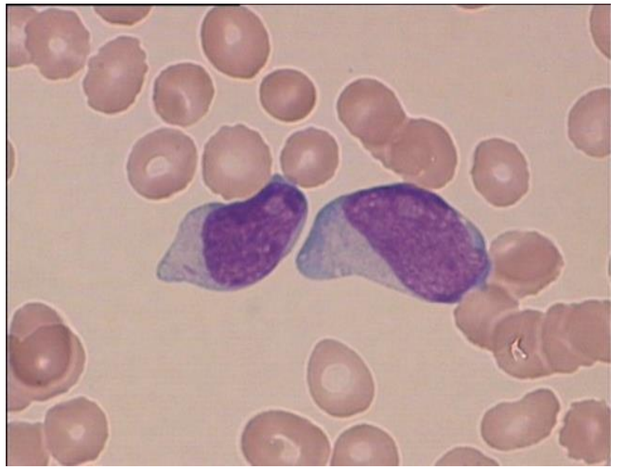
Mufti et al,2009



Blasti granulati



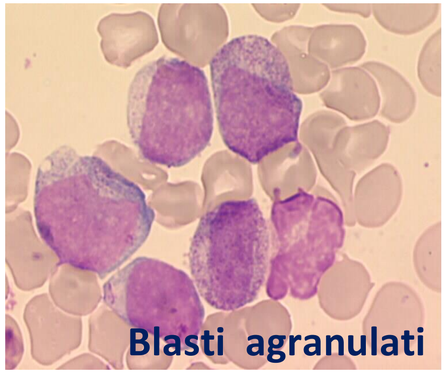
Blasti agranulati



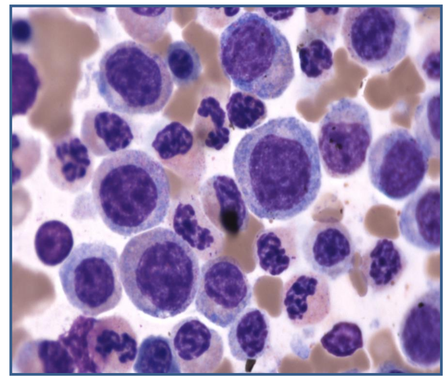
BLASTI VS PROMIELOCITI ATIPICI

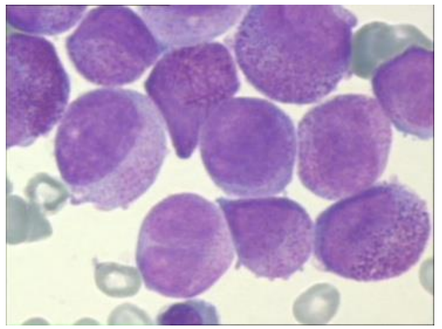
CRITERI MORFOLOGICI per la DEFINIZIONE dei BLASTI nelle MDS

MORFOLOGIA	Bl. agran	Bl.granulati	Prom.anormale	Promi. Displastico	Promi.normale
Dimensioni	15	30	25-30	25	25-30
N/C	alto	medio	baso	basso	basso
Basofilia citopl.	++	++		irregolare	+
Nucleo	rotondo centrale	rotondo centrale	eccentrico ovale	eccentrico ovale	eccentrico ovale
Cromatina	fine	fine	fine	fine grossolana	fine intermedia
Nucleoli	1-2	1-2	01-feb prominenti	1 prominente	01-gen prominente
Golgi	--	--	presente poco sviluppat	presente poco sviluppato	presente visibile
Granulazioni	---	<20	grossalani numerose	distribuzione irregolare	azurofili disperse
Corpi di Auer	+/-	+	fagoot's	--	-



Blasti agranulati





Promielociti atipici

Neoplasie Mielodisplastiche

Clinica
Citopenia

Diagnosi interdiscliplinare
Classificazione
WHO 5° /ICC
Diagnosi Non sempre facile

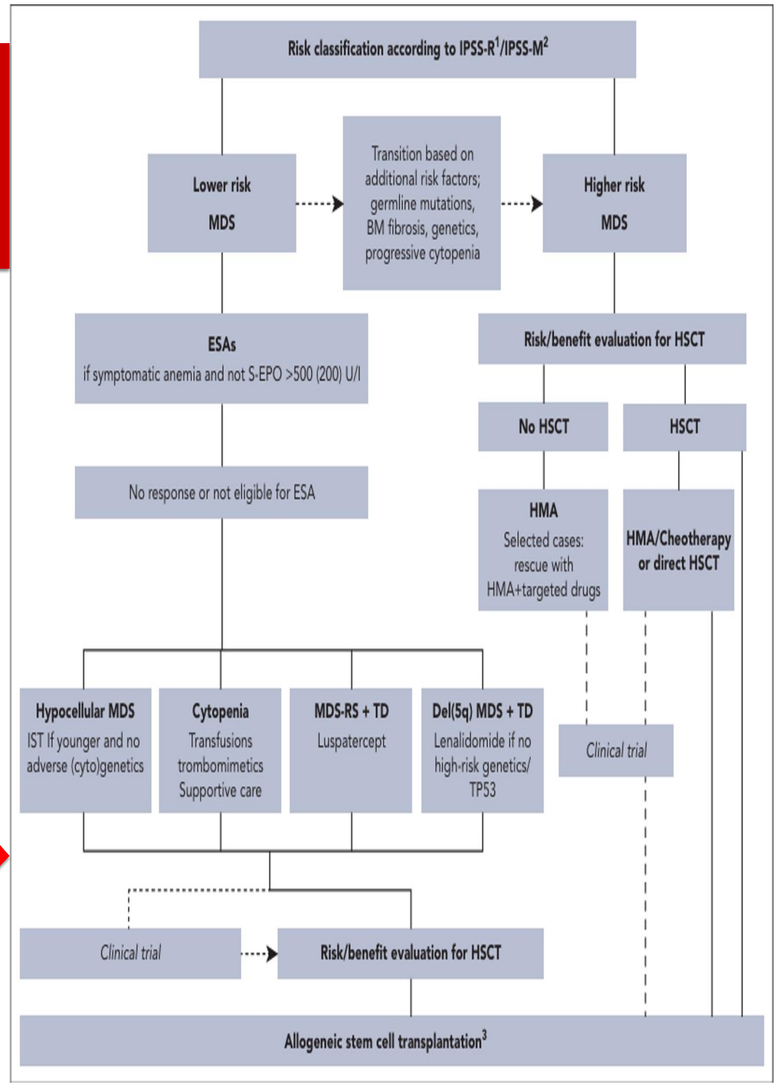
Decisione terapeutica
Non sempre facile

MYELODYSPLASTIC SYNDROMES IN THE AGE OF GENOMIC MEDICINE

Clinical decision-making and treatment of myelodysplastic syndromes

Eva S. Hellström-Lindberg[1] and Nicolaus Kröger[2]

[1]Department of Medicine, Karolinska Institutet, Center for Hematology and Regenerative Medicine, Karolinska University Hospital, Stockholm, Sweden; and
[2]Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany



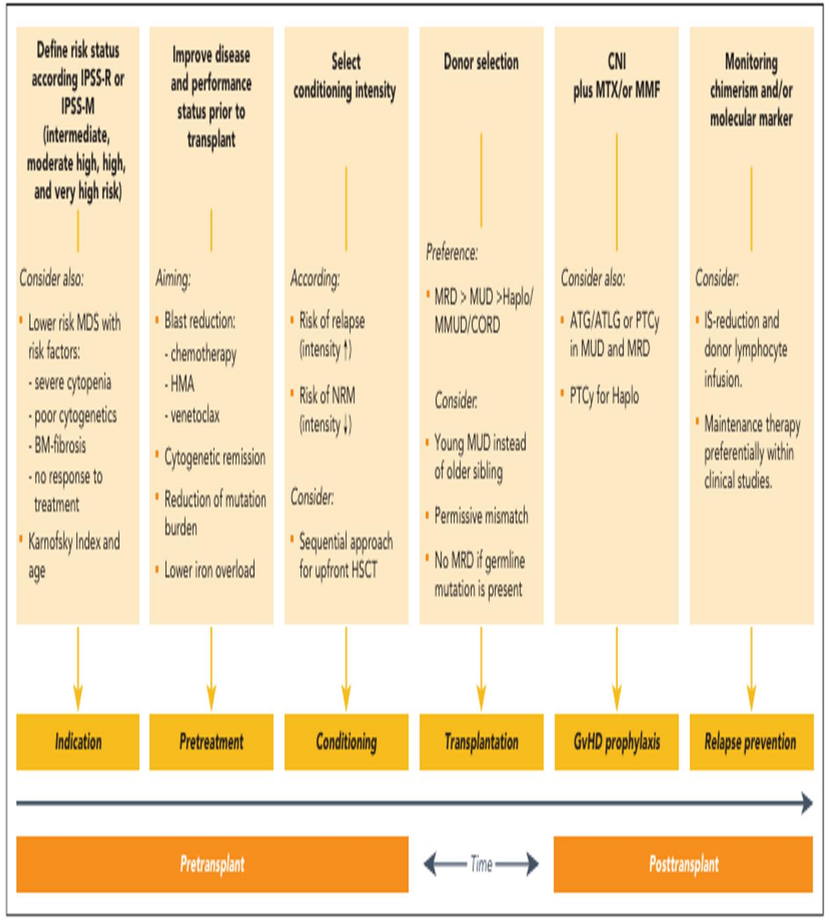


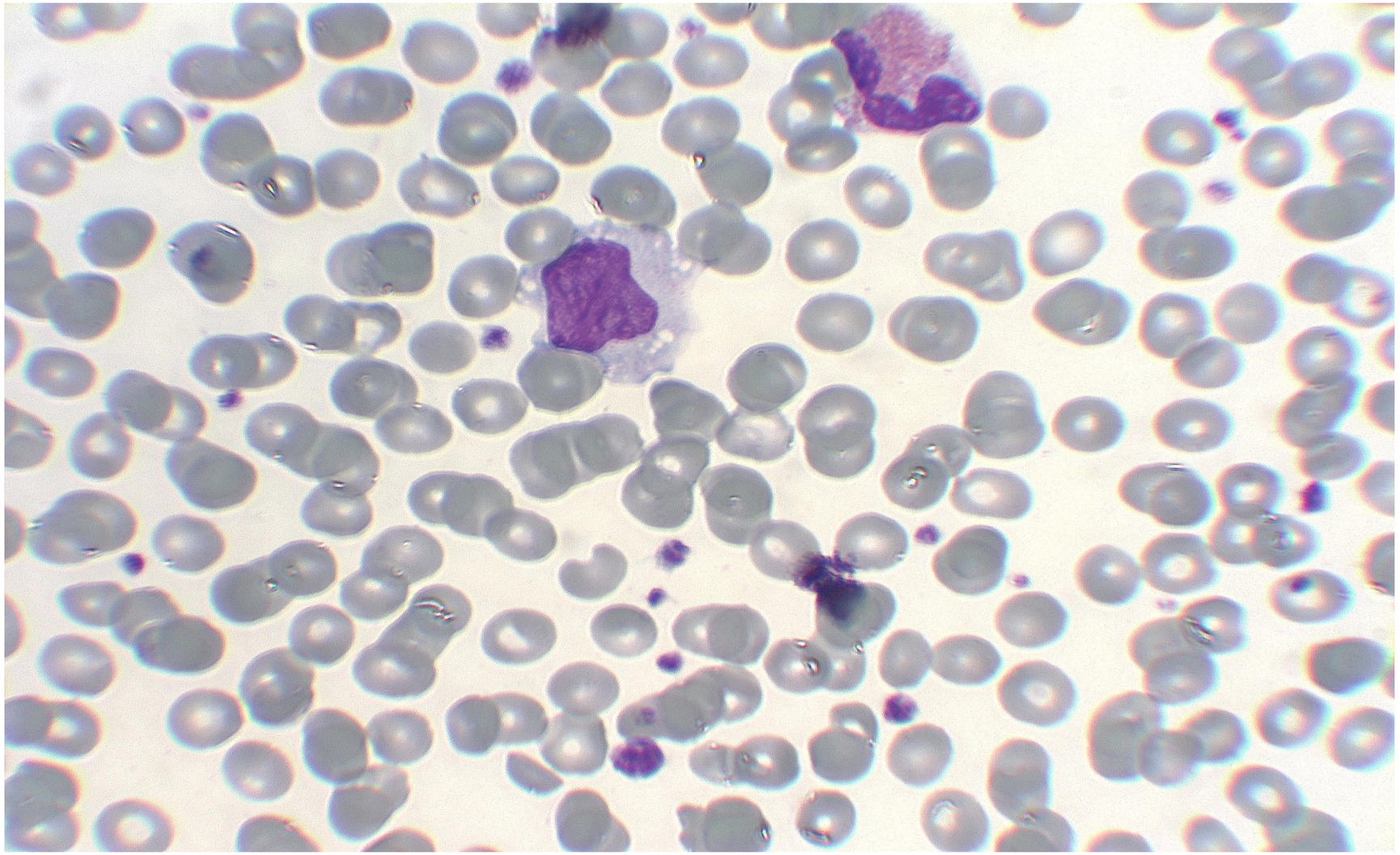
Figure 2. Main steps during allogeneic stem cell procedure for MDS.

Paziente di anni 54 non comorbidità di rilievo
anticorpi antigliadina positivi → sospetta celiachia
Attività professionale: Laurea in infermierstica →CELIO
Svolto missioni in Afganistan,Kossovo ,Iraq

Persistente Macrocitosi da circa 9 mesi
Hb 12,9gr/dl MCV 115fl RDW 20 Ht45%
GB 5750/mmc (N67% L 34% M9%) PLTS 200.000/mmc
Reticolociti 2% (va 30.000/µl/l)
LDH 230 U /L Dosaggio EPO 250 MU/L Ferritina 300 ng/dl Cupremia 80 µg/dl
Dos Vit B12 350 pg/dl Vit.B9 (Folato) 10 ng/dl
Esami strumentali : EGDS → gastrite dell' antro gastrico Hp Negativo
Colonscopia Negativa TC TB –Negativa per oragnomegalia

Fare striscio periferico?? Fare Aspirato Midollare ??

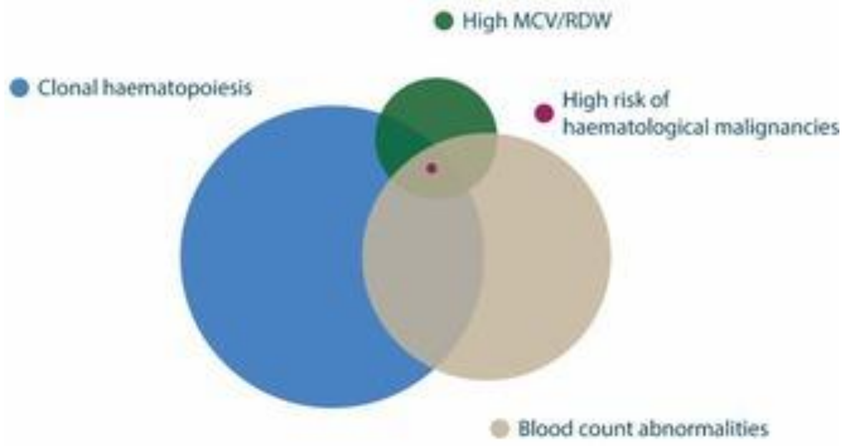
OSSERVAZIONE????

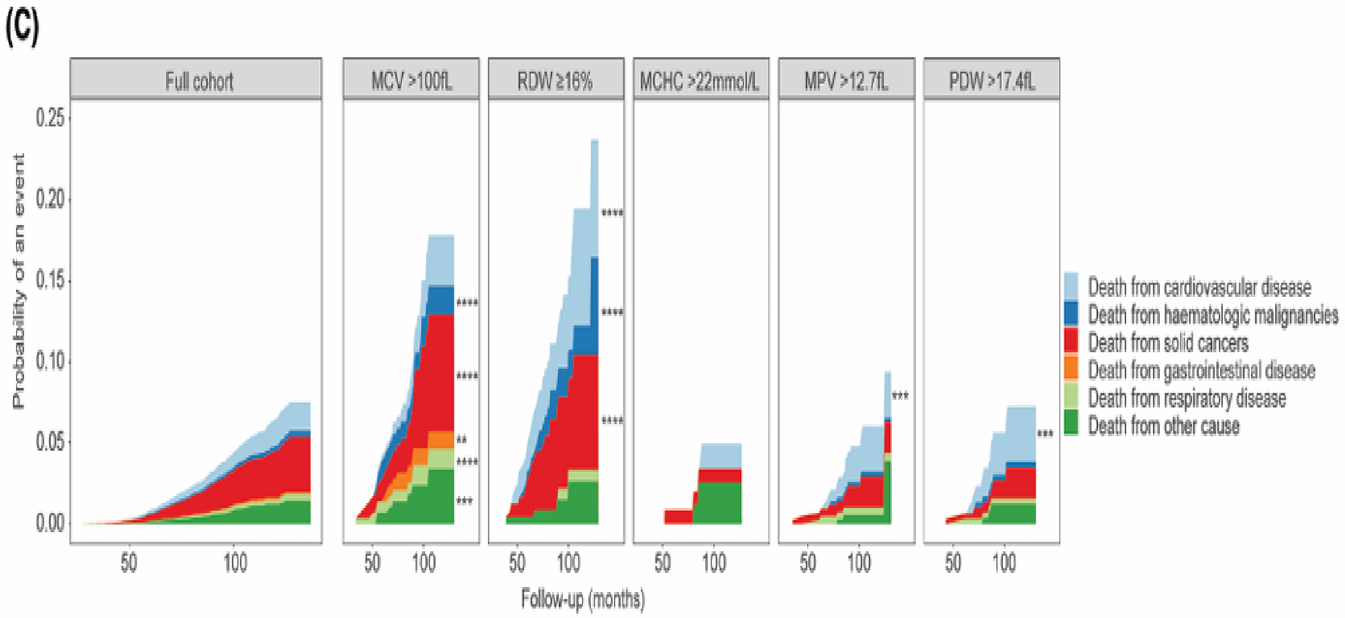


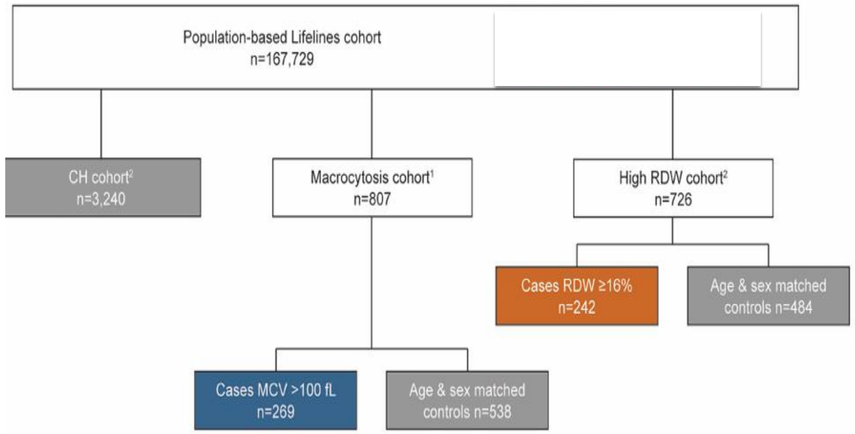
SVP MGG hpf 500x -→ rari monociti attivati ed eosinofili
Assenza di blasti

Clonal haematopoiesis associates with distinct cytometric changes of red blood cells and platelets

J. B. Salzbrunn[1] | I. A. van Zeventer[1] | A. O. de Graaf[2] | S. Klatte[3] | L. J. van Pelt[4] | P. Kamphuis[1] | M. G. J. M. van Bergen[2] | A. G. Dinmohamed[5,6] | B. A. van der Reijden[2] | J. Linssen[3] | J. J. Schuringa[1] | J. H. Jansen[2] | G. Huls[1]







Correlano con alterazioni morfologiche del SVP
MCV>100fl—> DMT3A ,SF3B1,TP53,PPMID Indicativo di rischio di evoluzione nelle CH (adverse health risk)
RDW>14,5%_-> *ASXL1*, *JAK2*, *SRSF2* , *U2AF1*
***MPV,PDW* →. *TET2* , *SRSF2* alterazioni morfologiche delle piastrine**
Elevata mortalità cardiovascolare

BJH 2025

Clonal hematopoiesis – mutation-specific adaptation to environmental change

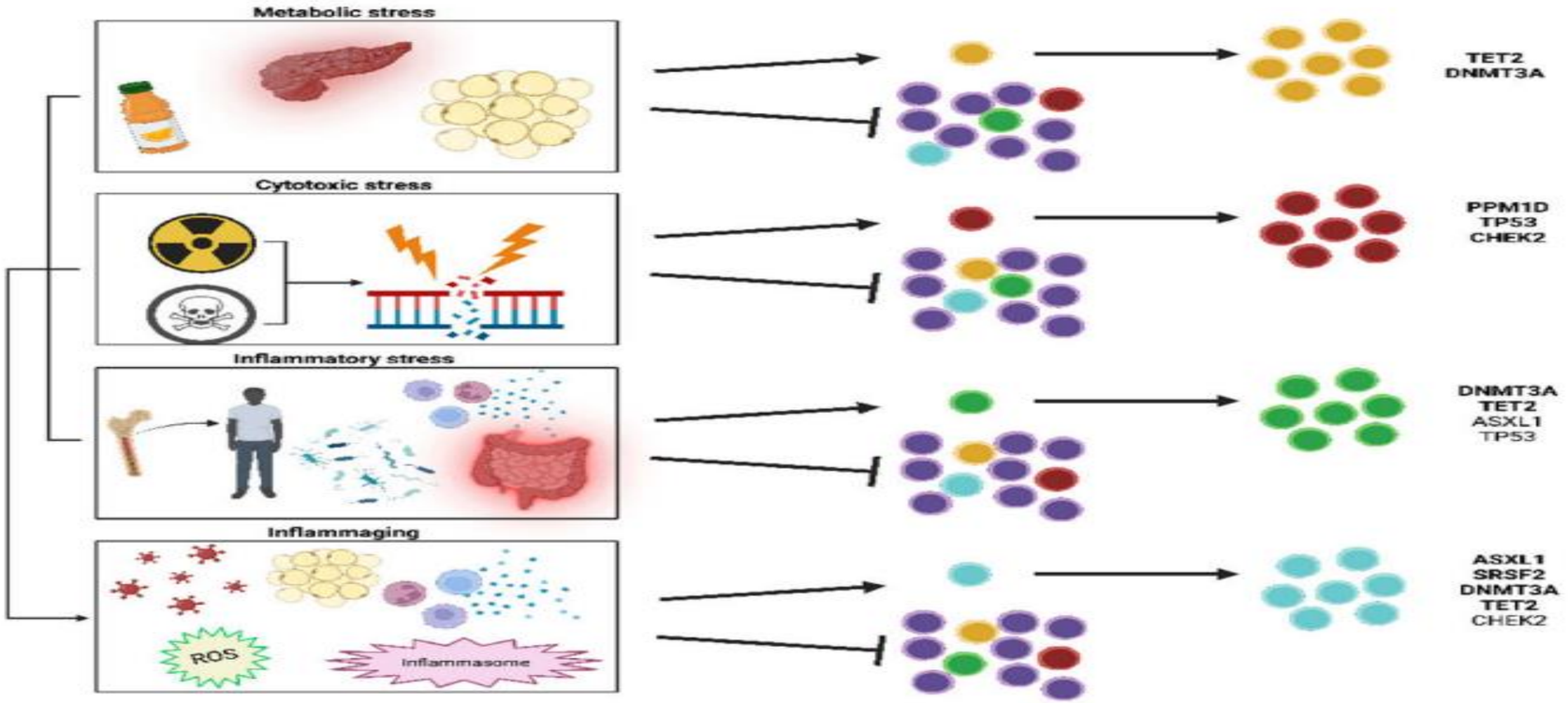
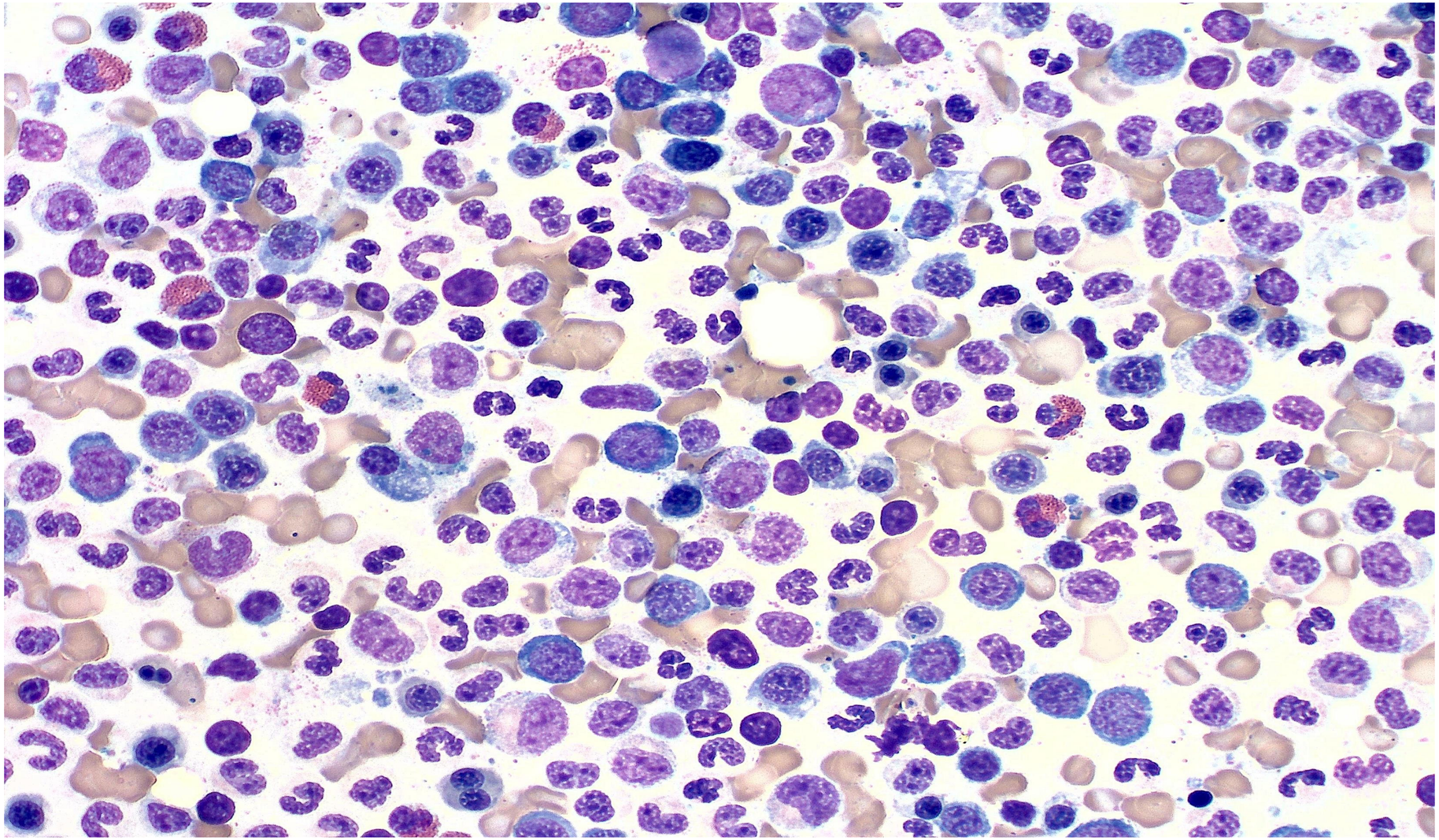
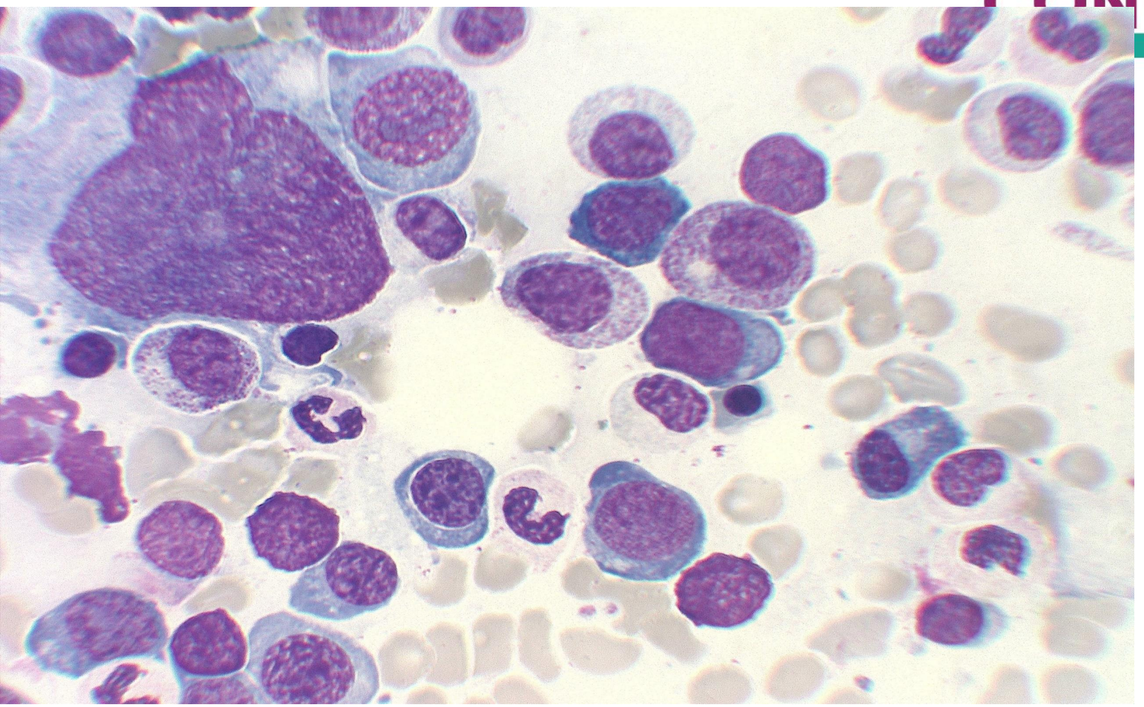
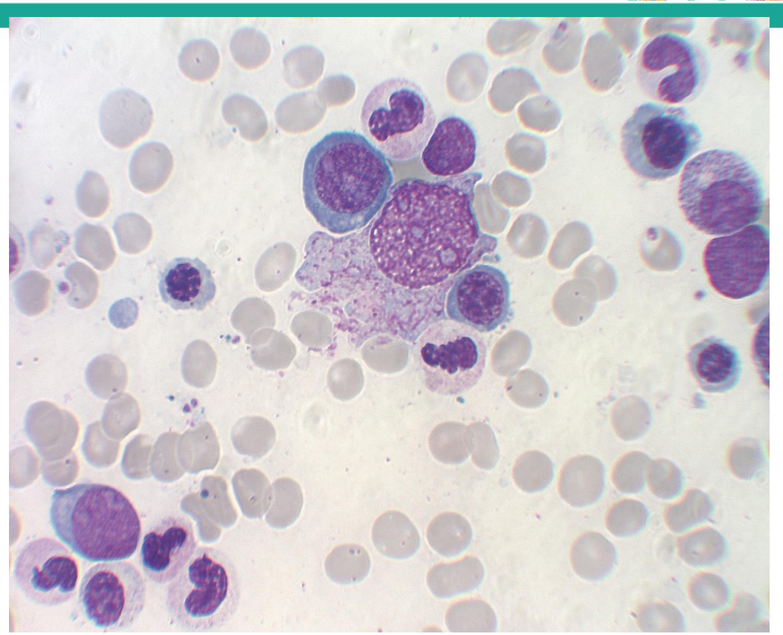


Figure 1: Environmental stressors promote mutation-specific clonal expansion.
Over an organism's lifetime, HSCs encounter cellular stresses which may induce somatic mutations in common driver genes. Depending on the context, somatic mutations may confer a selection advantage for certain clones to persist and expand. Environmental effects on clonal competition are mutation specific. Genotoxic stressors such as chemotherapy and radiation provide a selection advantage for clones bearing mutations in p53, PPM1D, and CHEK2, whereas infection and inflammation promote the expansion of clones with mutations in TET2 and DNMT3A. Studies on the metabolic effects of clonal expansion suggest that metabolites, like vitamin C, may impact the function of mutations, such as TET2.

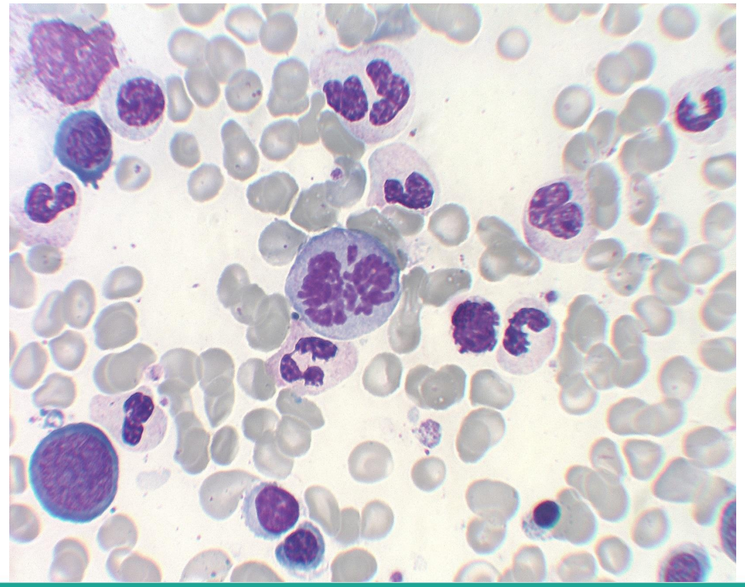


Apposizione Biopsia ossea AM hpf 500 x

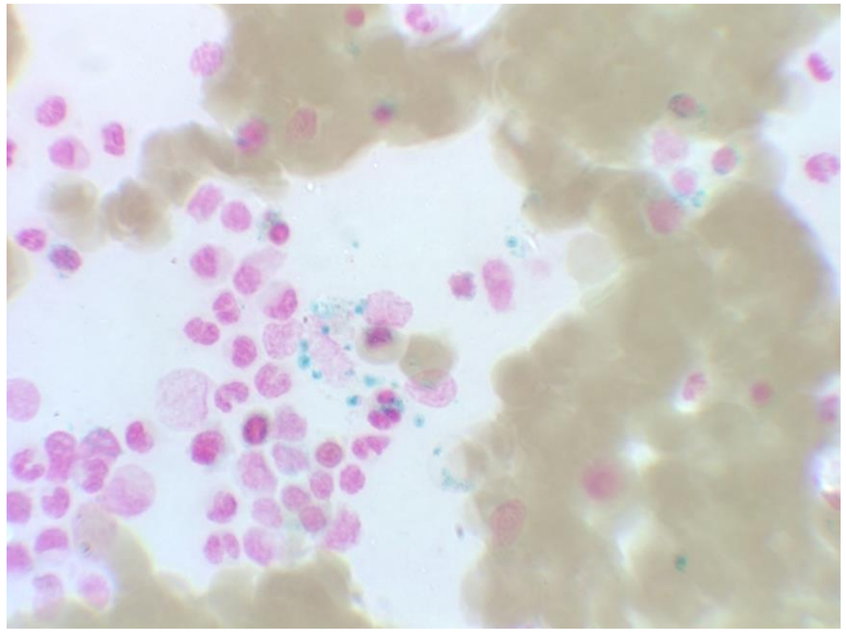


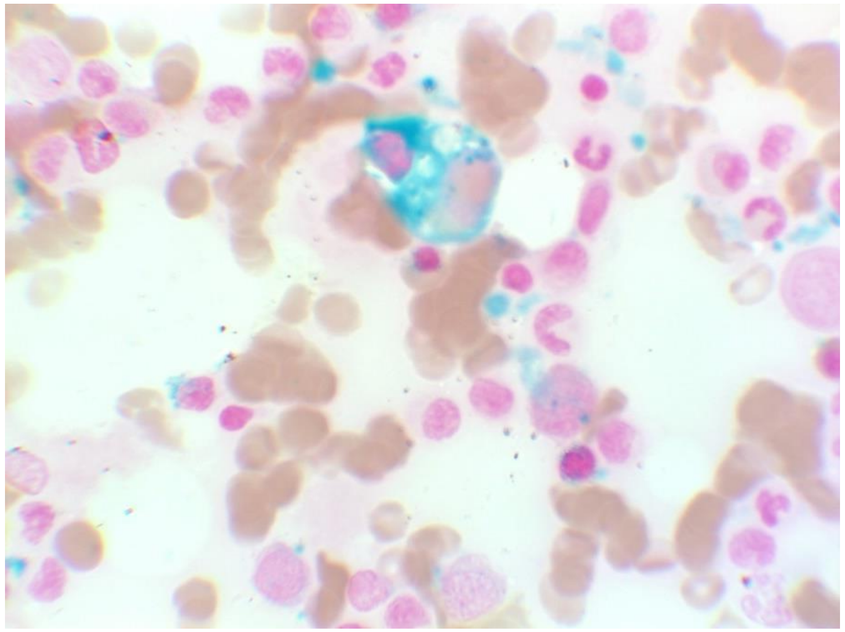


Cellularità **Aumentata (4) Megacariociti in numero normale (1-2 pcv)**
Istiociti >2% alcuni con aspetto Blu Mare
Mielogramma Er 30% Gr 36% L 15% Eos 5% Mastociti1% plasmacellule 4%
blasti agranulati 9%
Gr/Er 1,2%----→MDS iB1
Immunofenotipo : CD34/CD117 1,8%
BOM iperplasia eritroblastica con deviazione verso l' immaturità
Serie Granuloblastica normorapresentata Megacariociti in numero normale
immunoistochimiche hanno messo in evidenza la presenza di elementi ad 'habitus" blastico (CD34+/CD117+), costituenti meno del 5% della cellularità complessiva.
Assenza di fibrosi Mielodisplasia



COLORAZIONE BLU DI PRUSSIA





Abbondante ferro intramacrofagico
Sideroblasti ad anello 27%
Sideroblasti 20%

Citogenetica 46XY,
NGS DMT3A SF3B1 Mutato
EZH2 1,2%

Quale terapia ???
EPO??
Luspatercept(emoglobina stabile 12,9 gr/dl)
Osservazione ??

AM:
Mieloblasti 9%

CD34

MT3A
to

EZH2
sottosoglia
VAF1,2%

Emocromo Hb 12,9gr/dl M

M9%) PLTS 200000/mmc

QUALE DIAG

- **CD34+CD117+<5%**
- **NGS Mutazioni**

SF3B1 (K 700E) (VAF39,5%)
EZH2(1,2 %sottosoglia)

- **Cutt off Blasti??**

A) LB-MDS-RS(WHO2022
B) MDS with SF3B1 (ICC20
C) MDS iB1-RS

ERAPIA ??
nitoraggio stretto
miliare

T

AM: Mieloblasti 9% → **CD34+CD1171,8%+/BOM CD34/CD117 <5%** → **RS 27%** → **SF3B1 /DMT3A Mutato** → **EZH2 sottosoglia VAF1,2%**

Emocromo Hb 12,9gr/dl MCV 115fl RDW 20 Ht45% GB 5750/mmc (N67% L 34% M9%) PLTS 200000/mmc
rIPSS score 3 LOW MIPSS -1,39. LOW

QUALE DIAGNOSI ??

- **CD34+CD117+<5%**
-
- **SF3B1 (K700E)(VAF 39,5%) DMT3A(40,8%)**
  EZH2(1,2% sottosoglia)
- **Cutt off Blasti??**

A) LB-MDS-RS(WHO2022)
B) MDS with SF3B1 (ICC2022)
C) MDS iB1-RS

QUALE TERAPIA

A)Osservazione+monitoraggio stretto ricerca donatore familiare

B) ESA
C) Luspatercept
D) Ipometilante →SCT

MCV / RDW elevati

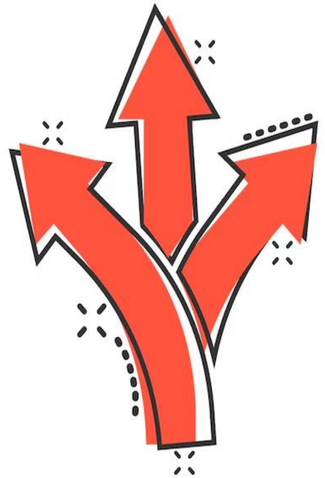
OPEN QUESTIONS

Risultati contrastanti??
Cut di blasti
NGS?
Basso rischio vs Alto rischio

- Diagnosi Morfologica -→ Blasti midollari 9% ---> MDS iB1?
- Sideroblasti ad anello 27%
- Immunofenotipo Blasti (CD34 Cd117 1,8%)
- BOM CD 34/ CD117 <5%
- Citogenetica Normale
- NGS SF3B1 mutato(39.5%) DMT3A(40,8%)
- EZH2(1,2%)
- M IPSS LOW???

???

???



Emocromo ottobre 26
Hg10,1gr/dl MCV19fl GB 4890/mmc
ANC3000/mmc)PLTS 359.000/mmc
AM → blasti 6%
BOM in corso
Citogenetica / NGS in corso

REFERTO INTEGRATO

DECISIONE TERAPEUTICA

Data: 25/11/2025 Ore: 14:52

Provenienza:
Pronto Soccorso

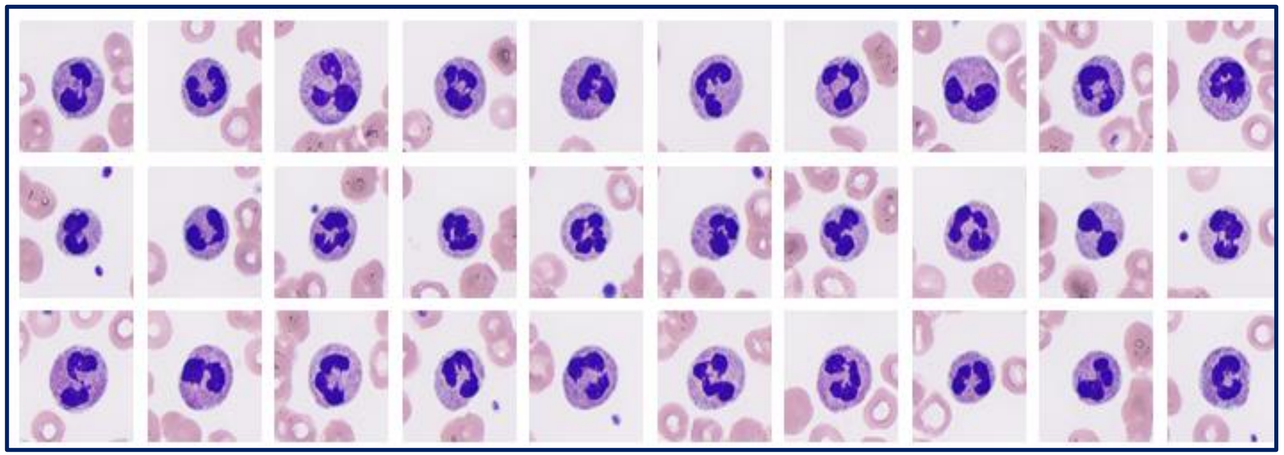
Globuli Rossi (RBC)	**2.1**	L	10^6/uL	4.4 - 6.0
Emoglobina (HGB)	**7.60**	L	g/dl	13.00 - 18.00
Ematocrito (HcT)	**23**	L	%	42 - 52
MCV	**109.00**	H	fl	85.00 - 98.00
MCH	**35.70**	H	pg	28.00 - 33.00
MCHC	**32.90**		gr/dl	32.00 - 37.00
RDW	**14.3**		%	11.6 - 14.6
Piastrine (PLT)	**153**		10^3/uL	140 - 400
PCT	**0.16**		%	0.12 - 0.36
PDW	**17.00**		%	
MPV	**10.60**		fl	7.00 - 11.00
Globuli Bianchi (WBC)	**3.98**	L	10^3/uL	4.30 - 10.80
Neutrofili%	**60.1**		%	45.0 - 74.0
Linfociti%	**34.1**		%	16.0 - 45.0
Monociti%	**2.6**		%	2.0 - 10.0
Eosinofili%	**3.0**		%	0.0 - 5.0
Basofili%	**0.2**		%	0.0 - 2.0
Neutrofili #	**2.39**		mille/mm^3	1.50 - 7.50
Linfociti #	**1.36**		mille/mm^3	1.00 - 4.50
Monociti #	**0.10**	L	mille/mm^3	0.20 - 1.00
Eosinofili #	**0.12**		mille/mm^3	0.00 - 0.70
Basofili #	**0.01**		mille/mm^3	0.00 - 0.20

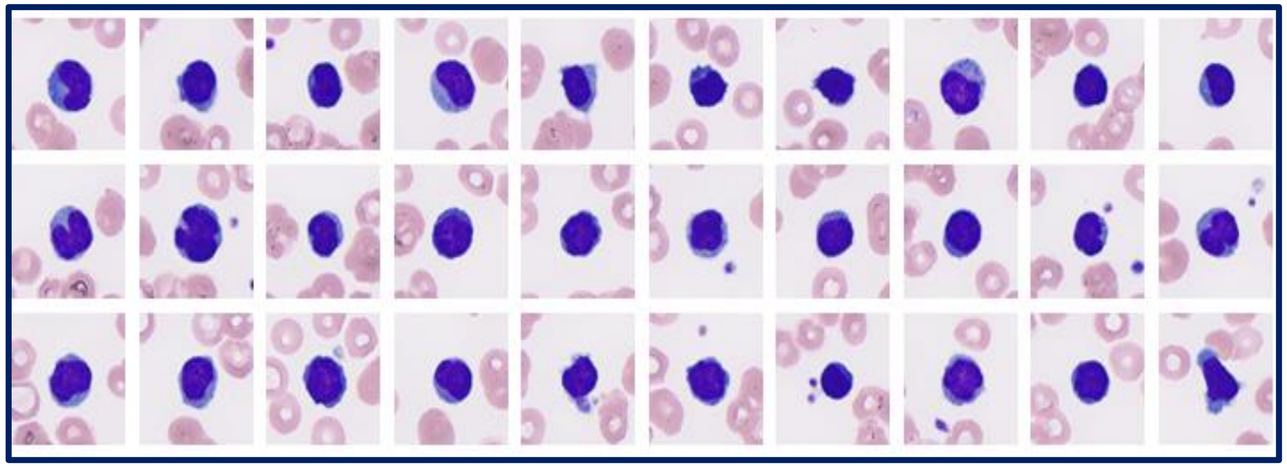
Uomo di 55 anni contadino
1 mese prima puntura da artropode comparsa di dispnea, dolore epigastrico con irradiazione al torace
astenia,febricola serotina , perdita di peso , parestesie bilaterali arti superiori ed inferiori artromialgia migrante, eritema cutaneo al torace ed estremità.
Videat ematologico → work up anemia macrocitica →sospetto MDS screenig reumatologico

Ricovero presso UOC Di Ematologia febbre (>39°C)elevata richiesta trasfusionale peggioramento Emocromo Hb 7.6 g/dL, (MCV109 fl Leucociti, 3.98×10³/µL, Piastrine 114×10³/µL reticolocitopenia.(0,2%) PCR 17.78 mg/dL
VES 83 mm/h , ferritina 1029 ng/mL ertropoietina 345 mIU/mL LDH250 U/l
TAI /TAD Negativi
EGDS pangrastrite HP positivo, iniziata terpia eradicante
TC TB **: micronoduli centrolobulari bilaterali con aspetto a vetro smerigliato, non linfoadenomeglaia, non splenomegalia.**

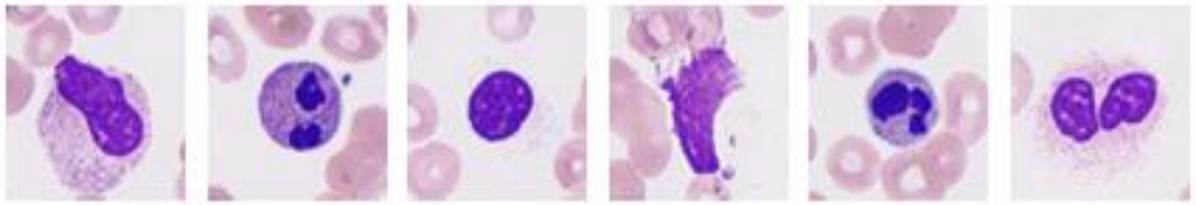
Screenig autoimmunità Negativo **screenig epatite** ab HBVc positivo, **Toxoplasma; CMV,EBV, PARVOVIRUS, HIV; HCV, quantiferon, Mycoplasma, leishmania NEGATIVO**
Borrelia IgM e IgG positive

Courtesy dott.ssa C Tatarelli & dott. E.Santacroce

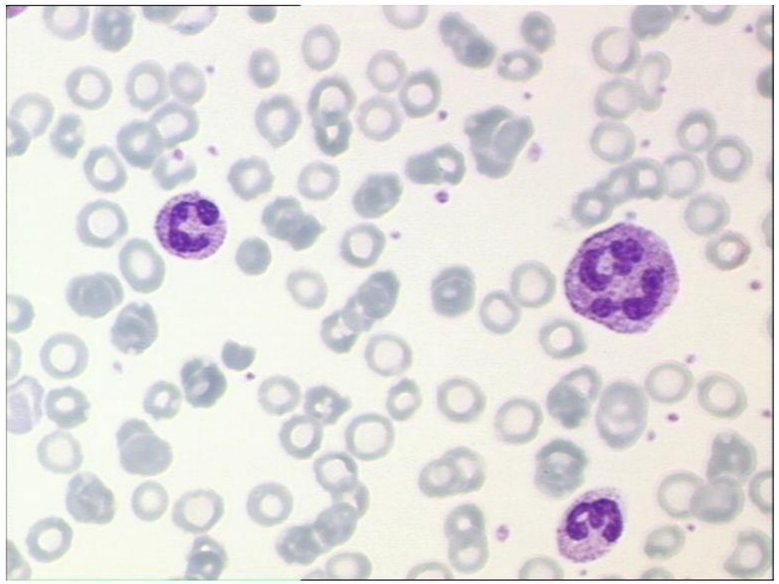




Cellule rotte



SVP MGG hpf 500x



SOSPETTO DIAGNOSTICO

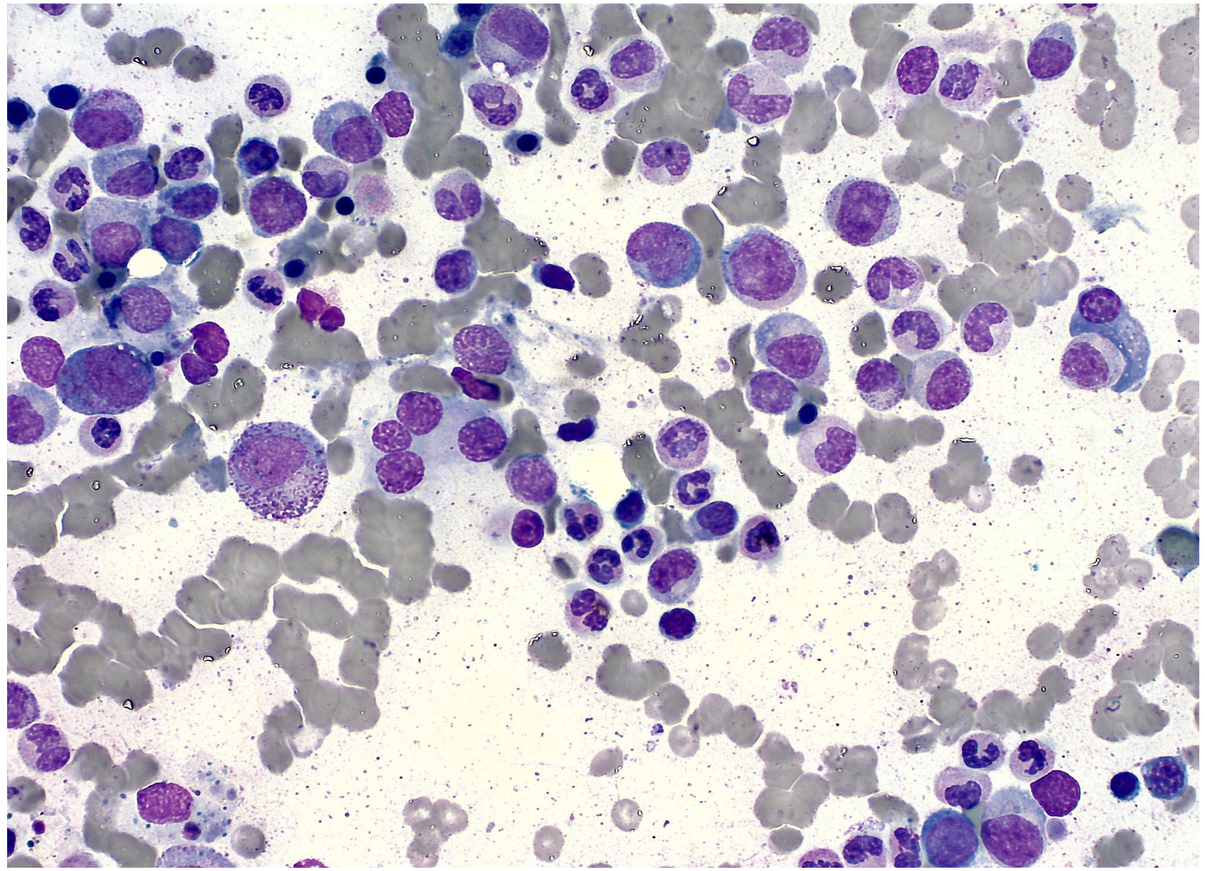
CITOPENIA
In corso di infezione
In corso di patologia autoimmune

EPN

ICUS

MDS acquiste





AM MGG hpf 500x

MORFOLOGIA MIDOLLARE

- Cellularità aumentata (4)
- Megacariociti in numero normale con aspetti evidenti aspetti di dismegacariocitopoiesi
- Istiociti >2% con lipofuscina

Conta differenziale su 500 cellule nucleate

Granuloblasti	50%
Eritroblasti	27%
Linfociti	15%
Prom +Monociti	3%
G/E ≈	2%

Eosinofili	2%
Plasmacellule	2%
Mieloblasti	2%
Mastociti atip.	1%

ALTERAZIONI MORFOLOGICHE

- Dimegacariocitopoiesi :megacariociti con nuclei multipli e separati,ipomononucleati
- Disgranulopoiesi: ipo-/agranularità, asincronia N/C, Bizzarrie nucleari
- Diseritropoiesi: megalocitosi, frammentazione nucleare, asincronia N/C
- Vacuolizzazioni: serie eritroide 3/25; granuloblastica 6/50

Mitosi eritroidi2/100 el nucleati

DESCRIZIONE

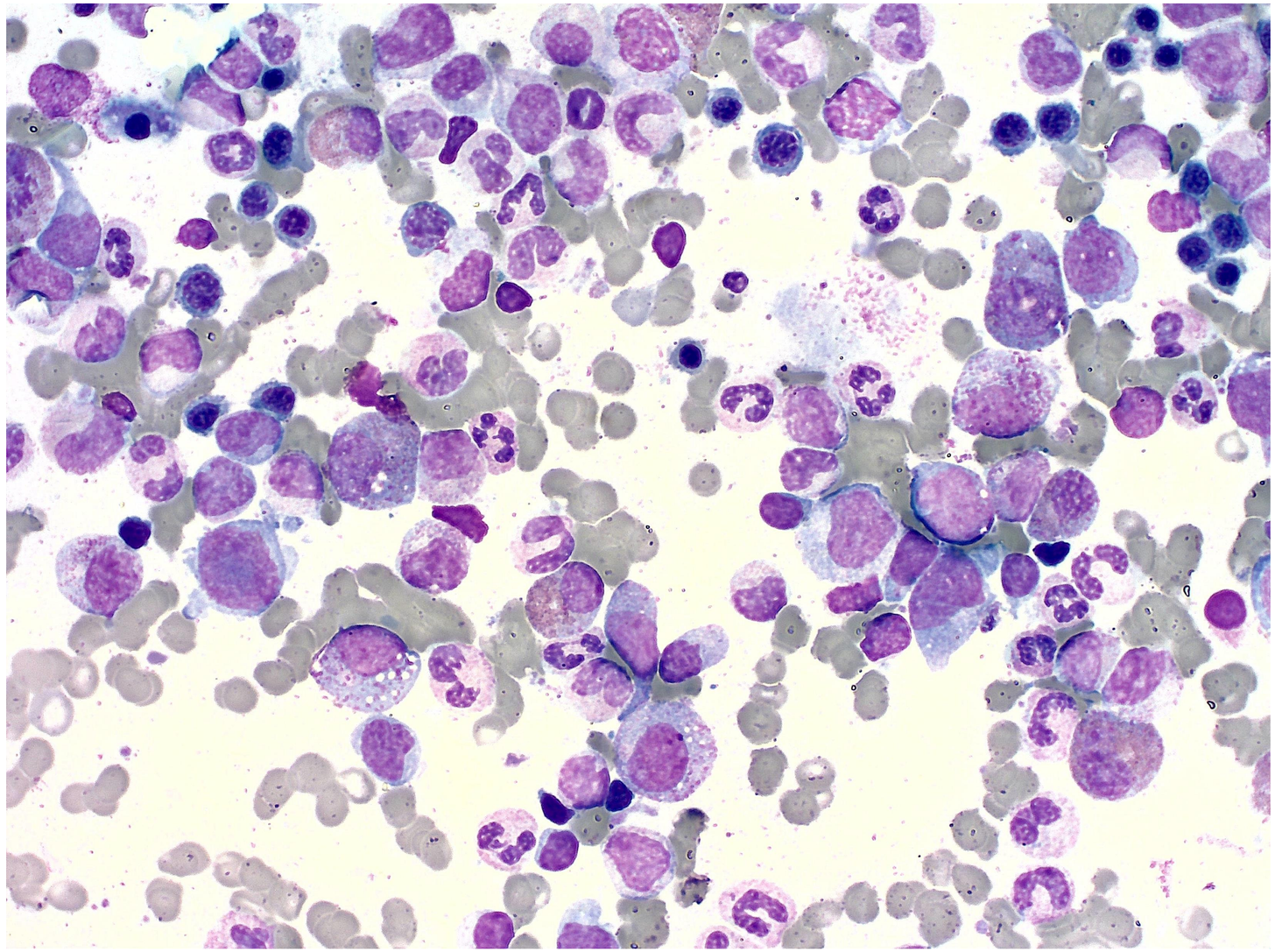
Lieve iperplasia della granuloblastica presente comn prevalenza della quota promielocitaria note evidenti disgranulopoiesi (el ipo/agranulati ,asicronia N/C,bizzarria nucleare a carico dei polimorfonucleati) alcuni elementi presentano vaucoli cipoplasmatici e nucleari

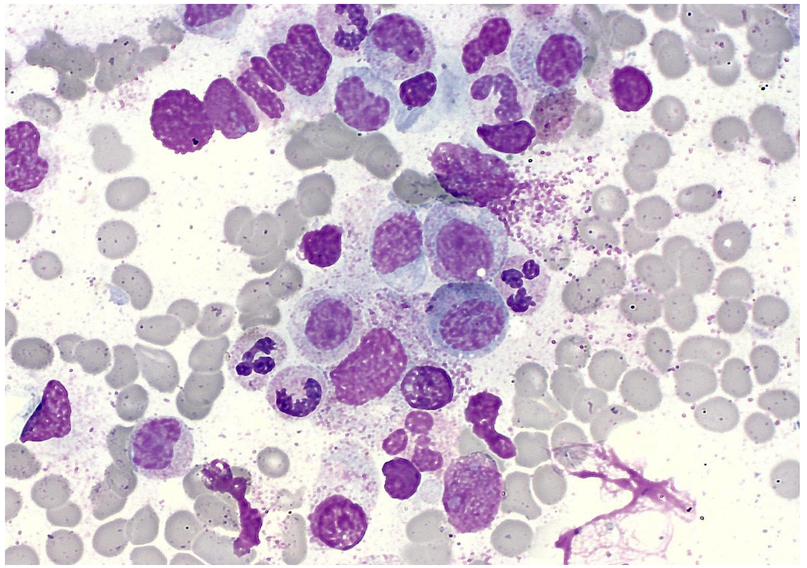
Serie eritroblastica con prevalenza della quota più immatura (left shift) caratterizzato da aspetti di diseritropoiesi (megalocitosi ,frammentazione nucleare asincronia N/C) Mieloblasti 2% A latere si segnala la presenza di mastociti atipici

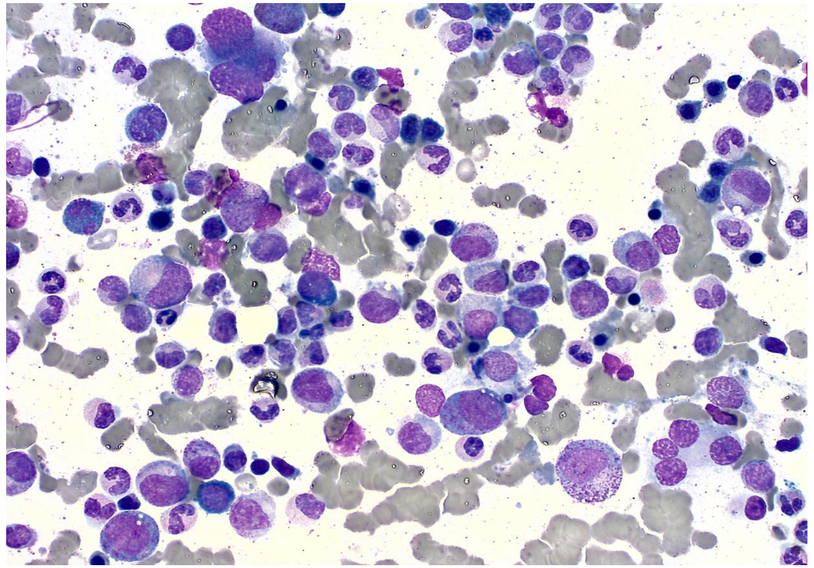
Conclusioni

quadro midollare con rappresentazione emopoietica trilineare, caratterizzata da aspetti di diplasia (>10% per filiera)

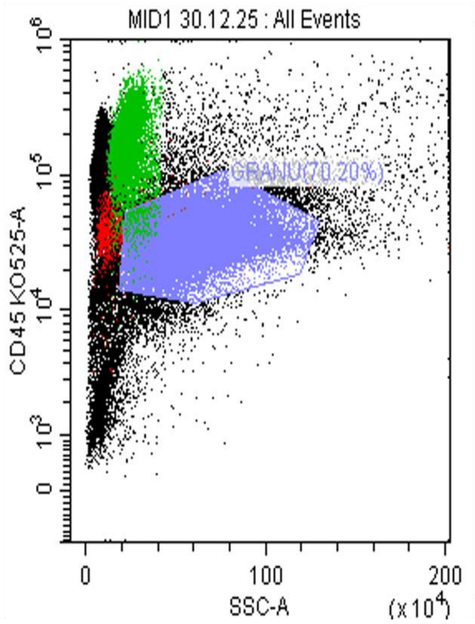
Neoplasia Mielodiplastica (NOS) da confermare con studio immunofenotipo , Ctogenetico.NGS



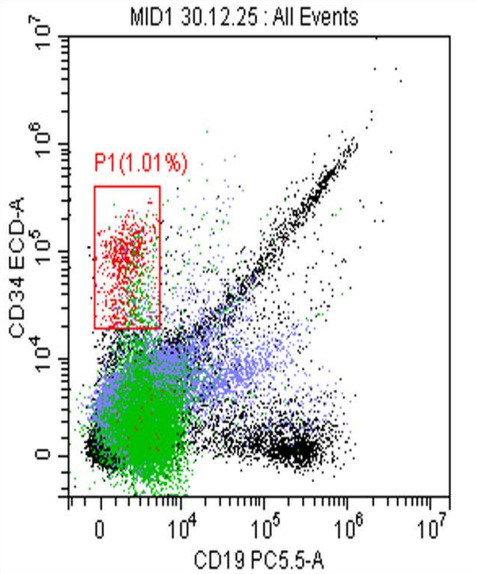




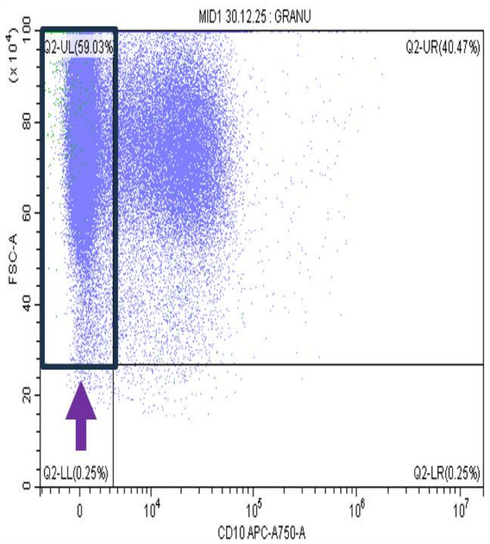
Immunofenotipo sangue midollare (1)



Il citogramma CD45/SSC presenta un ridotto side scatter suggestivo di ipogranulosità della popolazione granulocitica; tale dato viene considerato un indice di mielodisplasia

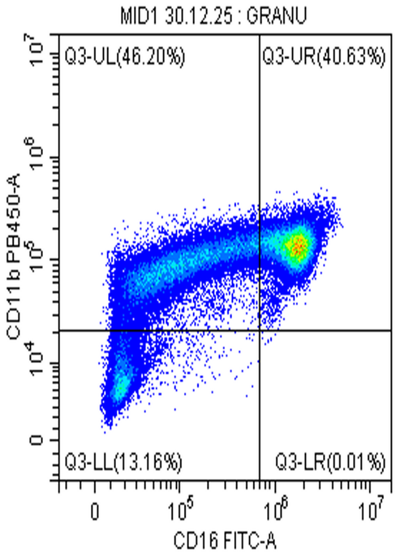


La quota di popolazione blastica CD34+ è pari a circa 1% della popolazione cellulare totale nucleata (v.n. <3%)

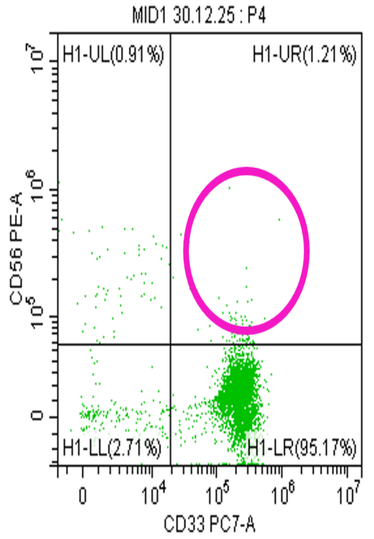


La popolazione granulocitaria presenta un deficit di espressione di CD10 pari al 59% (v.n. <10%); tale dato viene considerato un indice di mielodisplasia

Immunofenotipo sangue midollare (2)

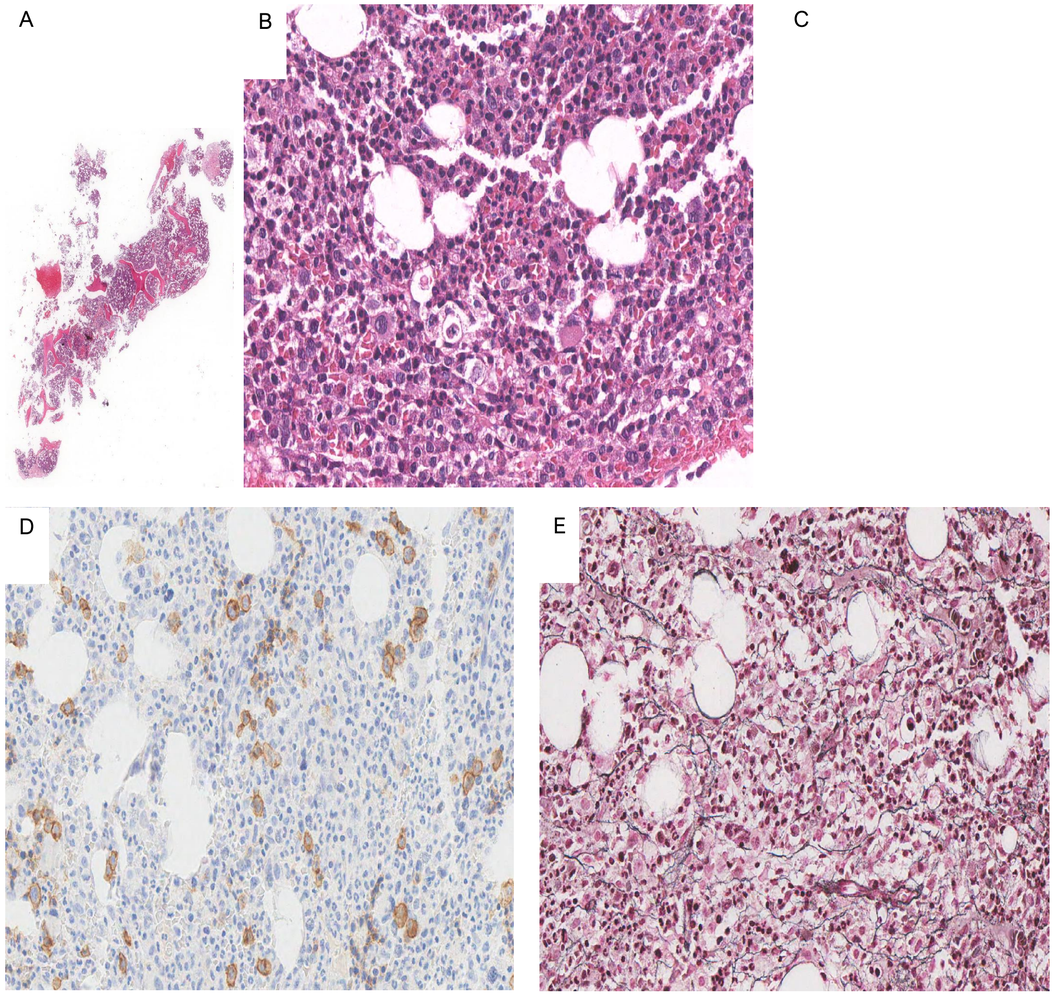


La maturazione granulocitaria studiata tramite espressione CD16/CD11b mostra solo una lieve anomalia nella maturazione tra mielociti e metamielociti; i promielociti a fenotipo CD16-/CD11b- rappresentano 13% della popolazione granocitica (v.n. <20%)



La popolazione monocitica CD14+ esprime, come da norma, l'antigene CD33 ad alta intensità e non presenta espressione aberrante di CD56

Courtesy of dr.R.Amodeo



BIOPSIA OSTEOMIDOLLARE

biopsia osteomidollare da spina iliaca postero superiore

DIAGNOSI:

Frustolo agaobioptico di tessuto osteomidollare della lunghezza di cm 1. Le cavità midollari mostrano unacellularità pari all'80% circa.

La popolazione ematopoietica è trilineare e si caratterizza per un aumento delle forme mieloidi segmentate a cui si associano segni di diseritropoiesi con aumento dei precursori ecaderina+ e aspetti di megaloblastosi e megacariociti aumentati in numero e spesso di taglia ridotta.

Si osserva una colorazione nucleare intensa per p53 nel 4-5% circa delle cellule.

La colorazione immunoistochimica per CD34 ha evidenziato una quota di blasti pari all'1-2% mentre quella per CD117 una quota di elementi immaturi pari al 3-4%. Si osserva un lieve incremento delle fibre reticolari interstiziali (MF-1). In sede interstiziale sono inoltre presenti alcuni piccoli linfociti T CD3+ (10-15%) occasionali piccoli linfociti B CD20+ (<5%) ed una quota di plasmacellule CD138+ (2-5%) con espressione citoplasmatica delle catene leggere kappa e lambda delle immunoglobuline in rapporto pari a circa 1.5:1.

Aspetti istologici da integrare con l'esame morfologico dello striscio di sangue midollare, i dati di aboratorio (parvovirus B19? HIV?) e le indagini citogenetiche e molecolari al fine di escludere il sospetto di neoplasia mielodisplastica.

Work up diagnostico

AM
Displasia trilineare
Vacuolizzazioni
Neoplasia
Mielodisplastica

→

BOM
Sospetta MDS
Escludere infezioni

→

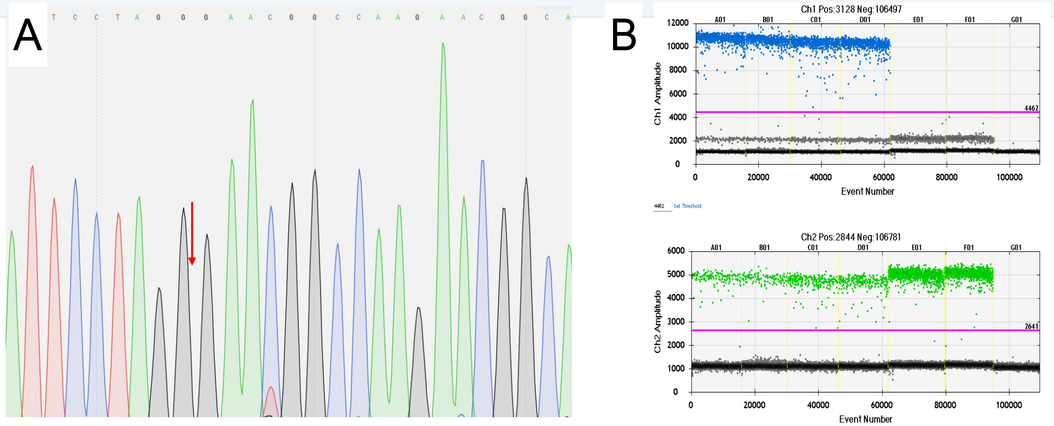
Citogenetica
46XY
NGS no
mutazioni

Maschio età >50anni contadino
Citopenia →anemia macrocitica →reticolocitopenia → trasfusione dipendenza(eritropoiesi inefficace)
Puntura da artopode
Sintomi multisistemici reumatologi/ neurologici
(Febbre Atralgie migranti parestesie)
TC Torace Micronoduli centrolobulari (vetro smerigliato)
infezione da Borrelia burgodorferi
sospetto S.Vexaxs?????

↓

Ricerca mutazione UBA1 ?????

- **UBA1 p.Met41Thr: VAF 86,5% nel sangue midollo e 60,8% nel sangue periferico**



A: p.Met41Thr (c.122T>C) mutation detected by Sanger sequencing on bone marrow blood.
B: p.Met41Thr variant allele frequency (VAF) quantified by ddPCR on bone marrow blood. Blue droplets represent the presence of mutant DNA, while green droplets represent wild-type DNA.

Decorso e complicanze

- **Trombosi della vena grande safena destra**
- **Otite media e mastoidite; Aspergillus niger isolato da tampone auricolare**

Terapia ed evoluzione

- **Prednisone 1 mg/kg**
- **Amoxicillina seguita da doxiciclina; terapia antifungina con isavuconazolo per 8 settimane**
- **Miglioramento di sintomi e indici infiammatori; persistenza di anemia macrocitica lieve (Hb 10,6 g/dL)**

- **Tipizzazione HLA per trapianto allogenico e arruolamento nello studio PAXIS (PACRITINIB)**

A clinical, histopathological, and molecular study of two cases of VEXAS syndrome without a definitive myeloid neoplasm

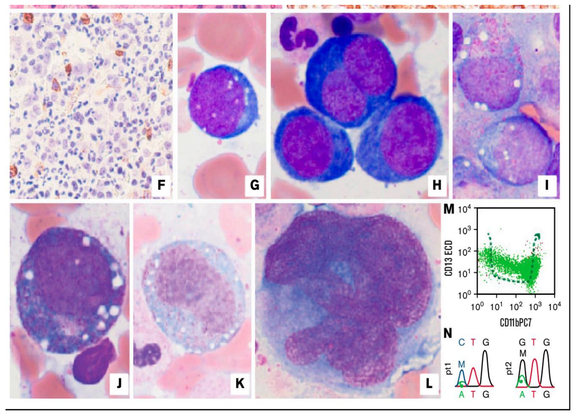
Peng Li,[1,2] Shobi Venkatachalam,[3] Daniela Ospina Cordona,[4] Lorena Wilson,[4] Tibor Kovacsovics,[3] Karen A. Moser,[1,2] Rodney R. Miles,[1,2] David B. Beck,[4] Tracy George,[1,2] and Srinivas K. Tantravahi[3]

[1]Division of Hematopathology, Department of Pathology, University of Utah Health, Salt Lake City, UT; [2]ARUP Laboratories, Salt Lake City, UT; [3]Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; and [4]National Human Genome Research Institute, Bethesda, MD

Table 1. Summary of clinical presentation and pertinent laboratory experiments

Overall clinical manifestations	Patient 1	Patient 2
Clinical presentation		
Fever	Yes	Yes
Cytopenia	Yes	Yes
Arthritis	Inflammatory polyarthritis	Joint pain only
Dermatitis	Neutrophilic dermatitis (Sweet syndrome)	Leukocytoclastic vasculitis
Pneumonitis	No	Yes
CBC (normal range)		
WBC, $\times 10^9$/L (4.3-11.3)	2.8	4.9
Hemoglobin, g/dL (14.8-17.8)	7.9	10.7
MCV, fL (81.2-96.6L)	110	114
Platelets $\times 10^9$/L (159-439)	121	71
ANC, $\times 10^9$/L (2.0-7.4)	2.5	2.9
Laboratory (normal range)		
C-reactive protein, mg/dL (0-0.8)	11.2	10.7
ESR, mm/h (0-10)	105	62
Bone marrow		
Circulating blasts (%)	0	0
Cellularity (%)	95	95
Blasts (%)	1	4
Myeloid/erythroid ratio	2.5	5.6
Ring sideroblasts (%)	5	0
Reticulin stain	MF 1/3	MF 1/3
Ancillary studies		
Karyotype	Normal	Normal
Variants by myeloid NGS panel (VAF %)	*PRPF40B* p.E399D (48.4)	None
UBA1 variants (VAF %)	p.M41L (67.3)	p.M41V (83.6)

Semiquantitative grading of reticulin fibrosis was performed using the MF grading system as described in the current WHO classification.[8]
ANC, absolute neutrophil count; CBC, complete blood count; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; MF marrow fibrosis; WBC, white blood cell.



re 1. Examination of peripheral blood and bone marrow biopsy specimens, as well as ancillary studies for both VEXAS patients. (A-B) There were no plasmic vacuoles or overt dysplastic changes in neutrophils (A) or monocytes (B) in peripheral blood (representative pictures from patient 1) Original magnification

Convergenza : Reumatologia vs Ematologia

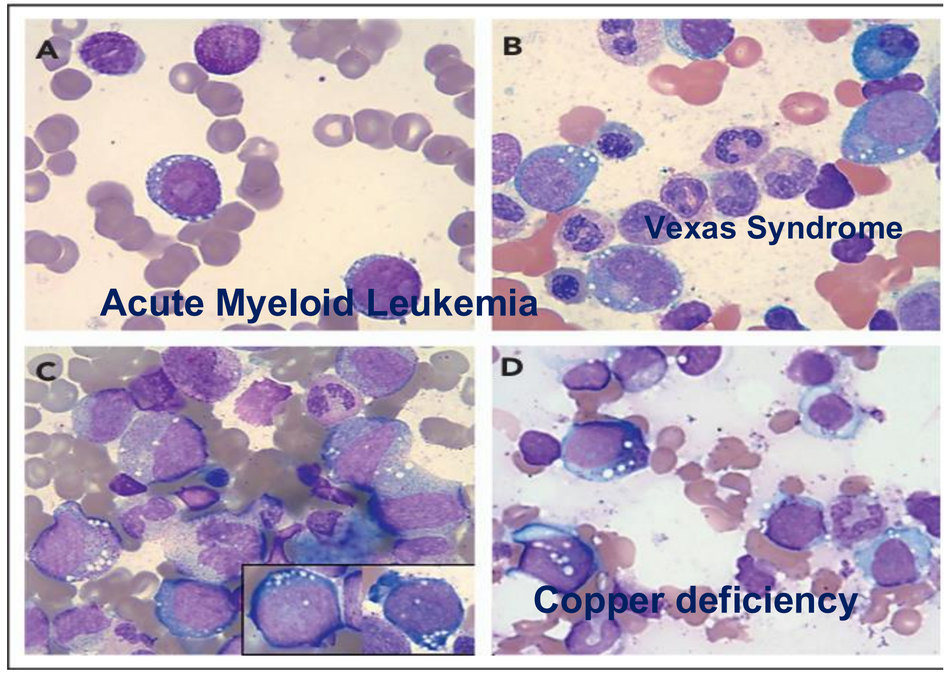
- ☐ Mutazione somatica misense Metp41 ter
- ☐ Autoinfiammazione
- ☐ Bone marrow failure (emopoiesi clonale)

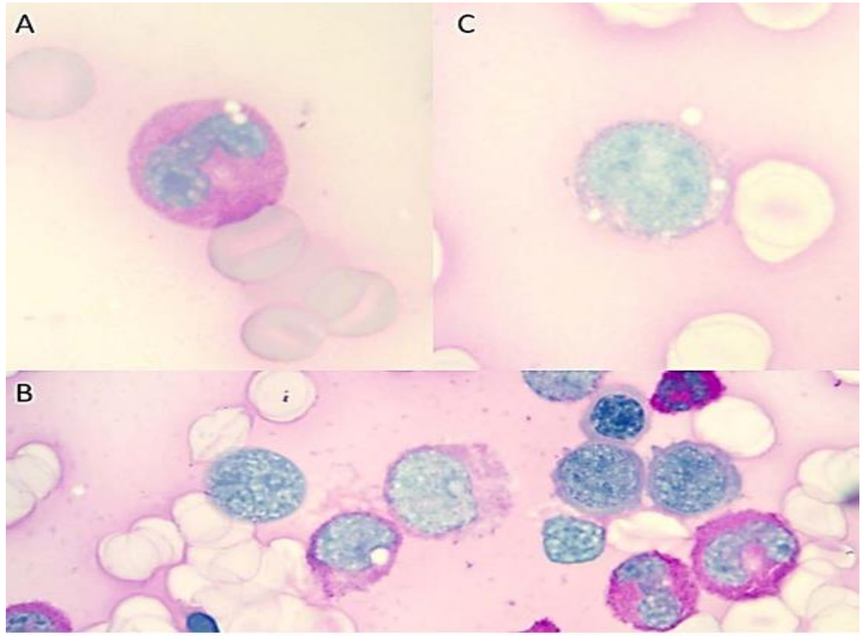
- **Vacuoles E1 enzyme X l inked autoinflammatory somatic**
- **VEXAS is a unique systemic autoinflammatory disease caused by somatic UBA1 mutations in the HSPCs that affect men exclusively**
- **Proteosomapatia →alterata ubiquitinazione→alterata degradazione delle proteine →vacuoli contenenti lipidi e frammenti di materiale mitocondriale**
- **-UBA1 è una mutazione non presente nelle MDS 25-55% dei pazienti sviluppano MDS**

TO THE EDITOR:

Vacuolization of hematopoietic precursors: an enigma with multiple etiologies

Carmelo Gurnari,[1,2] Simona Pagliuca,[1,3] Lisa Durkin,[4] Laila Terkawi,[1] Hassan Awada,[1] Sunisa Kongkiatkamon,[1] Misam Zawit,[1] Eric D. Hsi,[4] Hetty E. Carraway,[1,5] Heesun J. Rogers,[4] Valeria Visconte,[1,*] and Jaroslaw P. Maciejewski[1,5,*]





PAS positività citoplasmatica negli eritroblasti
vacuoli →negativi

Morphologically, ultrastructural studies reveal that the bone marrow vacuoles characteristic of VEXAS contain lipid droplets and disorganised organelles—such as mitochondrial fragments— indicating incomplete clearance of cellular constituents

R.Holden et all,2025 frontieres Immnunology

ISLH International Journal of Laboratory Hematology

CASE IMAGE OPEN ACCESS

Distinct Pattern of Atypical Megakaryocytes in VEXAS Syndrome

Andrew Y. Sung | Jackson W. Douglas | Olga K. Weinberg | Sharon K. Germans | Wei

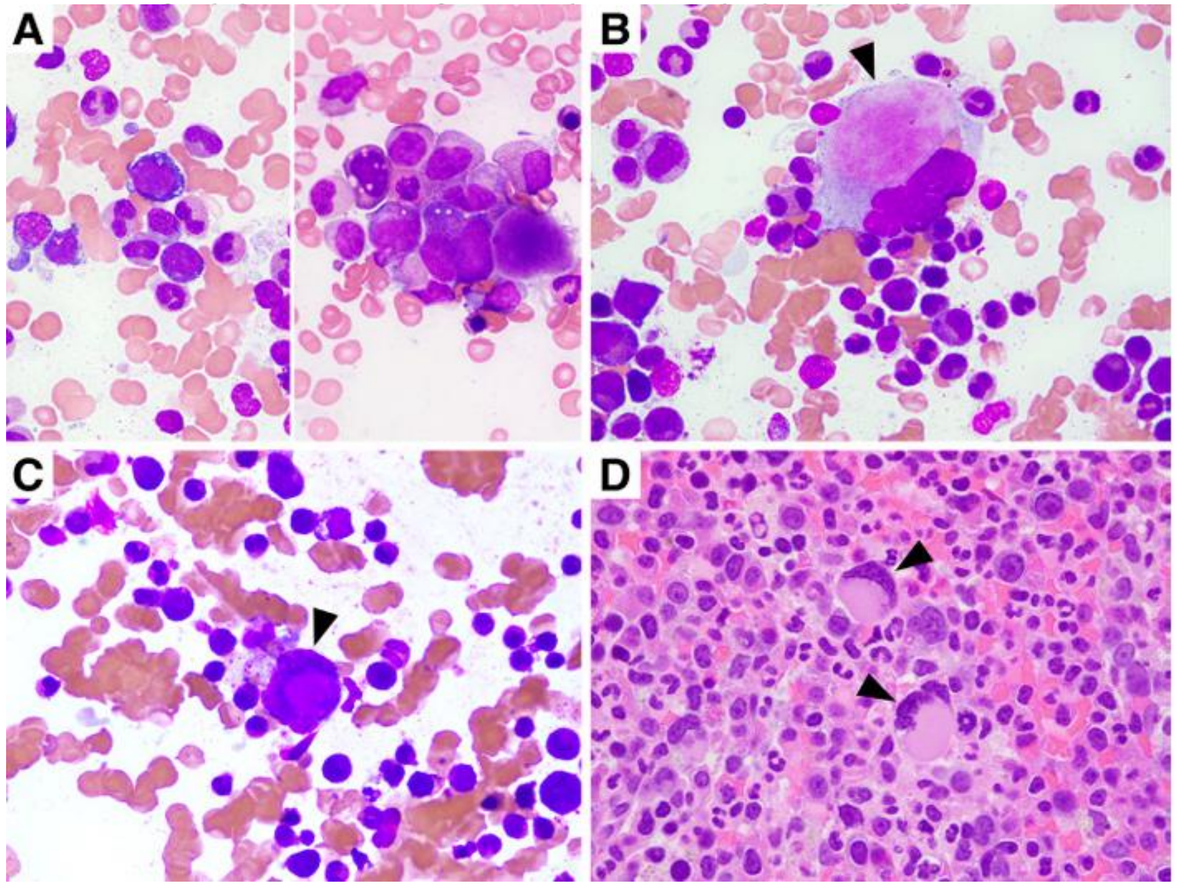
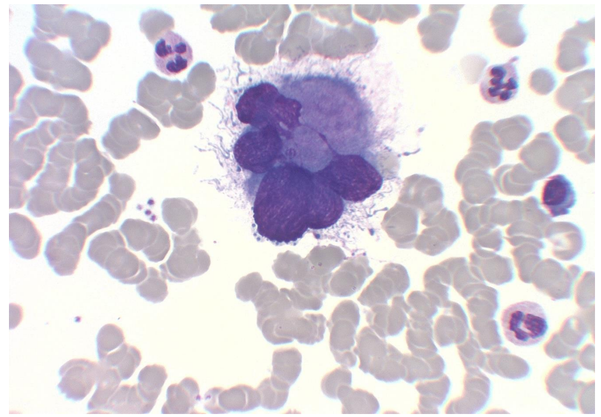
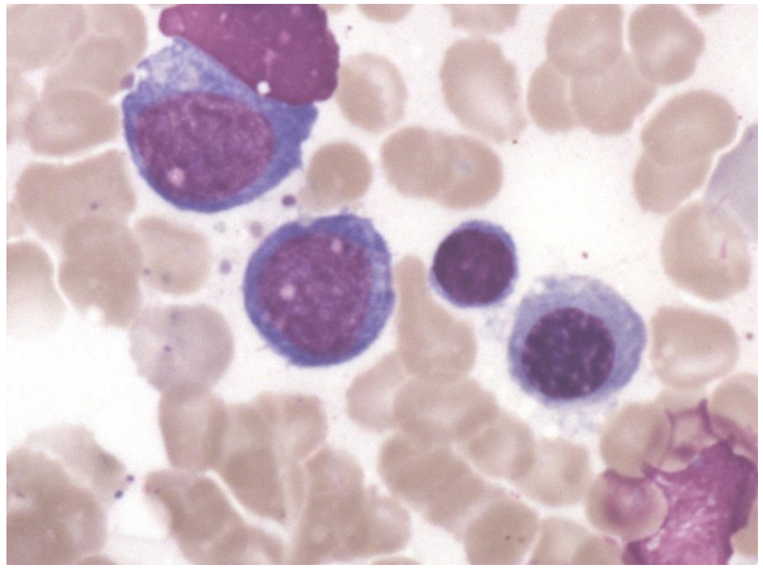
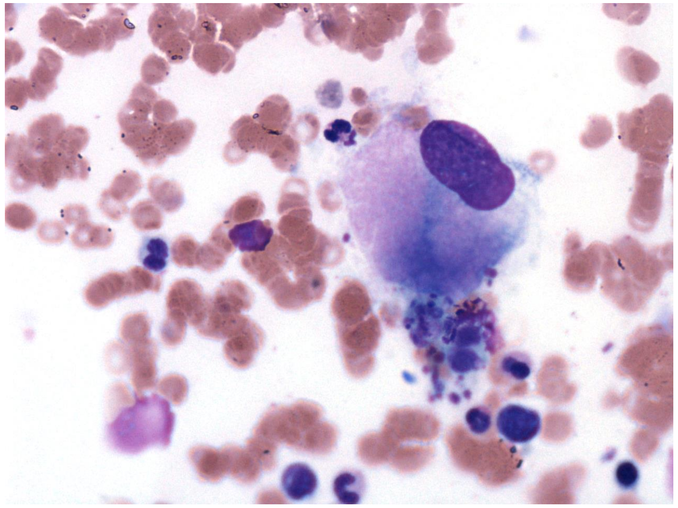


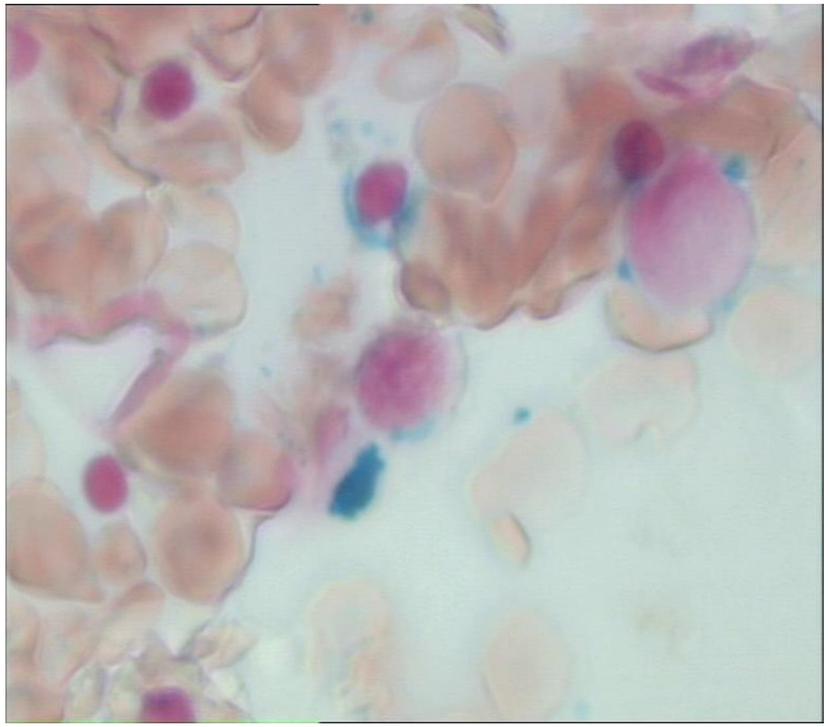
FIGURE 1 | Distinct pattern of atypical megakaryocytes in VEXAS syndrome. Bone marrow (BM) aspirate (A; Wright-Giemsa-stain, 1000x) showing vacuolization in erythroid precursors (left-A) and myeloid precursors (right-A). BM aspirate (B and C; Wright-Giemsa-stain, 1000x) and core biopsy (D; hematoxylin–eosin stain, 500x) showing megakaryocytes with condensed eosinophilic globule in the cytoplasm (arrowheads, B) and peripherally displaced, "wreath-like" nuclei (arrowheads, C and D).

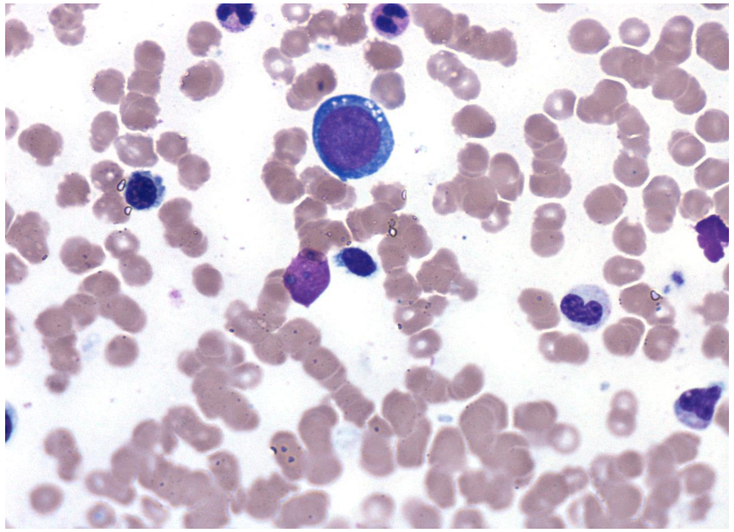


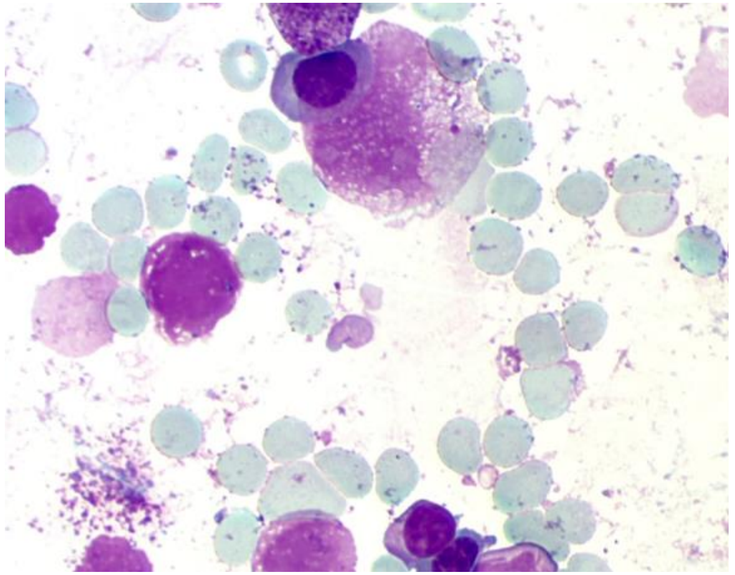
AM MGG hpf 500x
Dismegacariocitopoiesi in MDS











Sindrome di Pearson



zione/perdita del DNA mitocondriale→Mutazione somatica che compare precocemente durante l' embriogenesi

Danno catena respiratorioa mitocontriale

Alterazione δ aminolevulasi mitocondriale

CLINICA: ANEMIA MACROCITICA SEVERA esordio
Successuvamente sintomi gastroenterici
Malassorbimento
Insuff pancreatica acidosi lattica
ipotonia muscolare
Ritardo dell' accrescimento
Oftalmoplegia retipopatia
Atassia
BMF: citopenia trilineare(neutropenia,piastrinopenia)
AM presenza di vaculizzazioni citoplasmatiche nei precursori emopoietici , prevalenza negli eritroblasti left shift displasia trilineare

REVIEW Open Access

Pearson syndrome: a multisystem mitochondrial disease with bone marrow failure

Ayami Yoshimi[1*], Kaori Ishikawa[3], Charlotte Niemeyer[1] and Sarah C. Grünert[2]

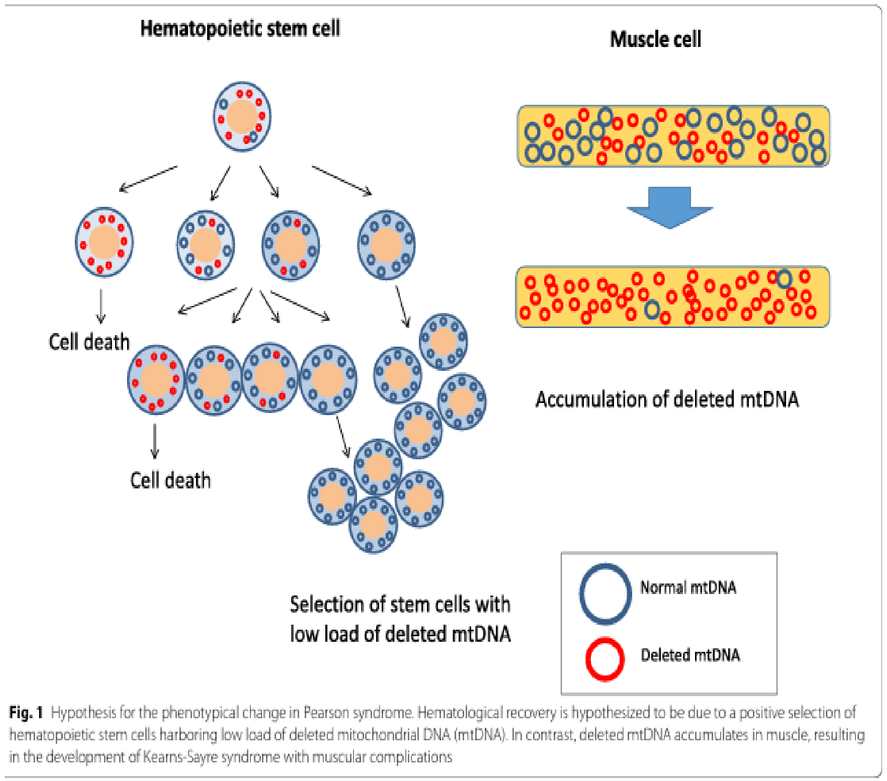
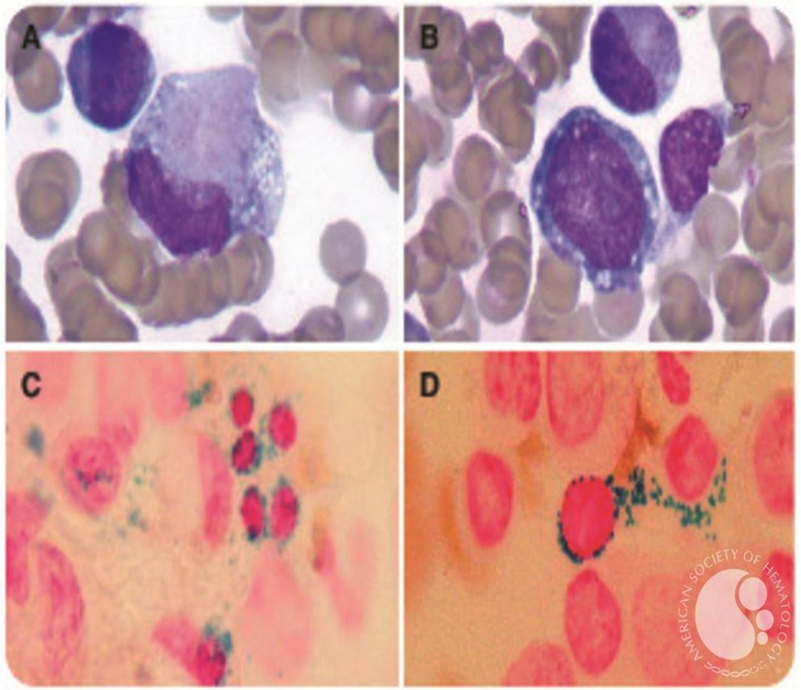


Fig. 1 Hypothesis for the phenotypical change in Pearson syndrome. Hematological recovery is hypothesized to be due to a positive selection of hematopoietic stem cells harboring low load of deleted mitochondrial DNA (mtDNA). In contrast, deleted mtDNA accumulates in muscle, resulting in the development of Kearns-Sayre syndrome with muscular complications

Primary mithocrondrial DNA deletion Syndromes



Sindrome di Pearson
Caratteristiche Morfologiche

TAKE HOME MESSAGE

Emocromo eseguito 1 anno prima dimostrava una macrocitosi (anamnesi accurata)

Indizi Confondenti???

- Puntura di artropode
- Infezione da Borrelia b.

(auto)infiammazione???

- Artralgie parestesie rash
- Infiltrati polmonari
- Citopenia

MDS ???

Anemia severa macrocitica reticolocitopenia

- Aspirato midollare/ BOM aspetti di displasia trilineare
- vacuolizzazioni citoplasmatiche

Non patognomoniche ma suggestive

- **Citogenetica 46xy NGS no Mutazioni**

UBA1 mutato

S.Vexas

American College of Rheumatology Guidance Statement for Diagnosis and Management of VEXAS Developed by the International VEXAS Working Group Expert Panel

Arthritis & Rheumatology Vol. 78, No. 3, March 2026, pp 509–522

When to consider testing for somatic *UBA1* variant

Pre-test probability is higher for MALES compared to FEMALES, for patients OLDER THAN 50 YEARS, and when ACUTE PHASE REACTANTS are ELEVATED

Typical Disease Features

Inflammatory:

- Fever of unknown origin
- Auricular and/or nasal chondritis
- Neutrophilic dermatosis or urticaria-like lesions(Bx)
- Leukocytoclastic vasculitis (LCV) or leukocytoclasia (Bx)
- Non-infectious periorbital swelling
- Recurrent, non-infectious inflammatory eye disease
- Non-infectious ground glass or nodular pulmonary infiltrate
- Unprovoked or recurrent thromboembolic disease
- Steroid dependency[4]

Hematologic:

- Vacuoles in myeloid or erythroid precursor cells on marrow aspirate
- Macrocytosis[1] or macrocytic anemia
- MDS or myelodysplasia
- Thrombocytopenia[2]
- Monocytopenia[3]
- Lymphopenia

Less Common Disease Features

- Erythema nodosum (Bx)
- Recurrent urticaria / urticarial plaque
- Injection site reaction to anakinra
- Inflammatory arthritis
- Vasculitis (any size), relapsing / recurrent or with lack of response to SOC
- Pericarditis / Myocarditis
- Exudative pleural or pericardial effusion
- Testicular inflammation
- Sensorineural hearing loss
- Atypical or opportunistic infection including nontuberculous mycobacterial infection
- Nephrotic syndrome with renal amyloidosis (Bx)
- Interstitial nephritis (Bx)

Figure 1. When to consider testing for VEXAS. A list of typical and less common disease features of VEXAS are presented to help guide clinicians regarding when to consider testing for acquired mutations in *UBA1*. Bx, biopsy confirmation required; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LCV, leukocytoclastic vasculitis; MCV, mean corpuscular volume; MDS, myelodysplastic syndrome; SOC, standard of care; VEXAS, vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome.

GRAZIE

Prof.ssa V. Santini



FISiM

ER CONGRESSI