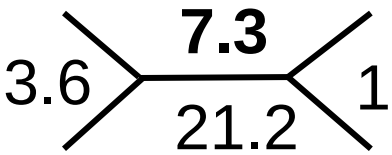
# Cases
# BM and FJ

October 11, 2011

# Case 1, BM

- History: 65 yo F with **pancytopenia**
- CBC:



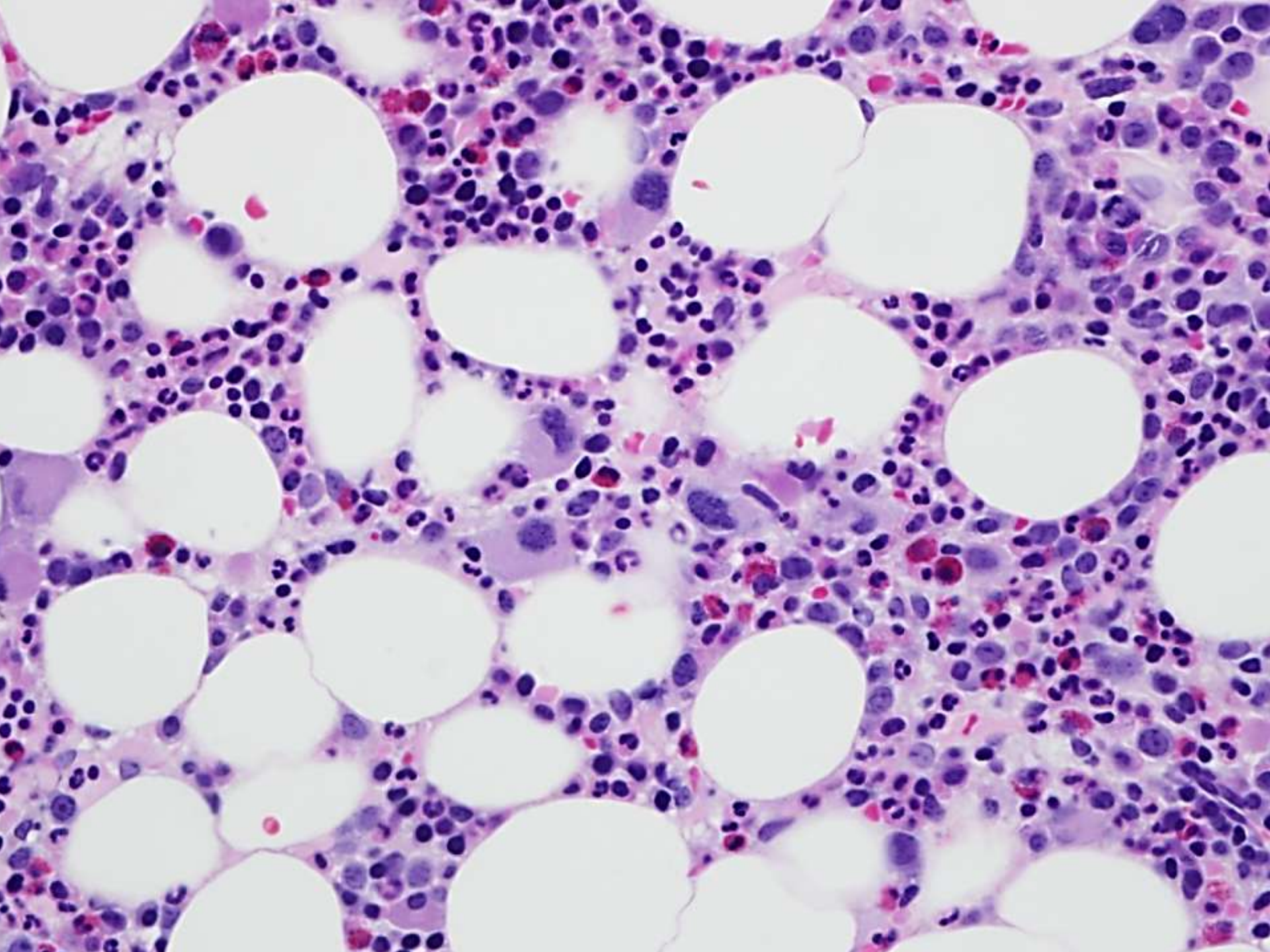

131, **MCV=100.3 fL**, RDW=25.7 %

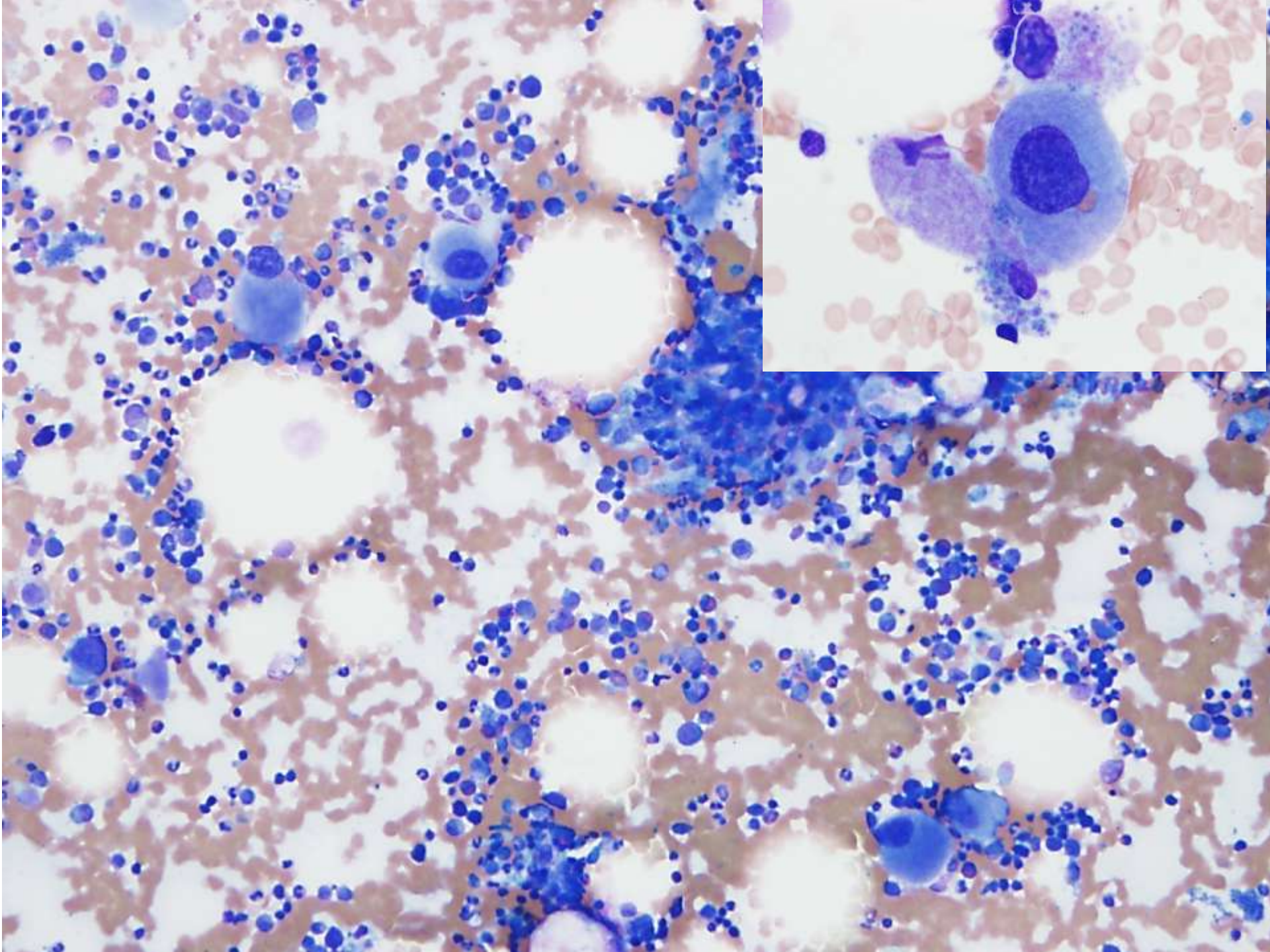
| | |
|---|---|
| Neutrophils | 56.8 % |
| Lymphocytes | 35.0 % |
| Monocytes | 6.0 % |
| Eosinophils | 2.1 % |
| Basophils | 0.1 % |

# Differential diagnosis

**Pancytopenia with macrocytic anemia**:

- -Vitamin B12 and folic acid deficiency
- -Drugs
- -Toxins (e.g. alcohol)
- -Liver and thyroid disease
- -Autoimmune hemolytic anemia
- -Cold agglutinin disease
- -Primary bone marrow failure:
  - -aplastic anemia
  - -myelodysplastic syndromes





# Bone marrow aspirate

| CELL | RESULT (%) | REFERENCE RANGE |
|---|---|---|
| • Blasts | 1.4 | (0.0 - 2.0) |
| • Promyelocytes | 2.8 | (2.0 - 8.0) |
| • Other granulocyte precursors | 43.2 L | (50.0 - 70.0) |
| • Erythroid precursors | 33.0 H | (20.0 - 25.0) |
| • Lymphocytes | 10.0 | (10.0 - 15.0) |
| • Eosinophils | 8.0 H | (1.0 - 3.0) |
| • Basophils | 0.6 | (0.0 - 1.0) |
| • Monocytes | 0.0 | (0.0 - 1.0) |
| • Plasma cells | 1.0 | (0.0 - 3.0) |
| M:E Ratio | 1.4 | (1.2 - 5.0) |

# Additional studies

- Iron stain:

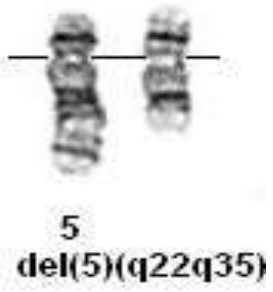
  -decreased iron storage. No ring sideroblasts.

- Flow cytometry performed on the bone marrow aspirate

  -unremarkable.

- Cytogenetic studies:

  46,XX,del(5)(q22q35)[16]/46,XX[4]




- FISH confirmed del 5q

# Summary of findings

- Peripheral blood :
  - -pancytopenia,
    - -macrocytic anemia
- Bone marrow:
  - -hypercellular for age
  - -megakaryocytic dysplasia
- Cytogenetics:
  - -isolated del(5) (q13q33)

- Inefficient hematopoiesis:

**Myelodysplastic syndrome**

# Differential diagnosis for MDS with del(5q)

- *MDS with isolated del(5q)*

  -**older female**

  -**anemia** (usually macrocytic) +/- other cytopenias

  -**thrombocytosis** or normal platelet count

  -**myeloblasts <5%** in BM, **<1%** in PB

  **-isolated del(5q)**

- *Therapy related myeloid neoplasms: t-AML, t-MDS, and t-MDS/MPN*

  -history of **chemotherapy and/or radiotherapy**

  -**cytopenias**

  -**dysplastic changes** (usually in all lineages)

  -cytogenetic changes more complex

# Diagnosis

- Myelodysplastic syndrome, best classified as isolated del(5q) in the appropriate clinical context.

# Case 2, FJ

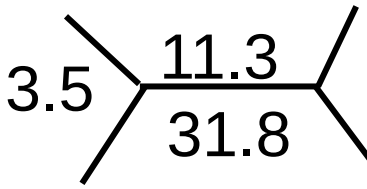
# Case 2

Hx:

- 73 yo F
- In the last months experienced episodes of tremendous fatigue

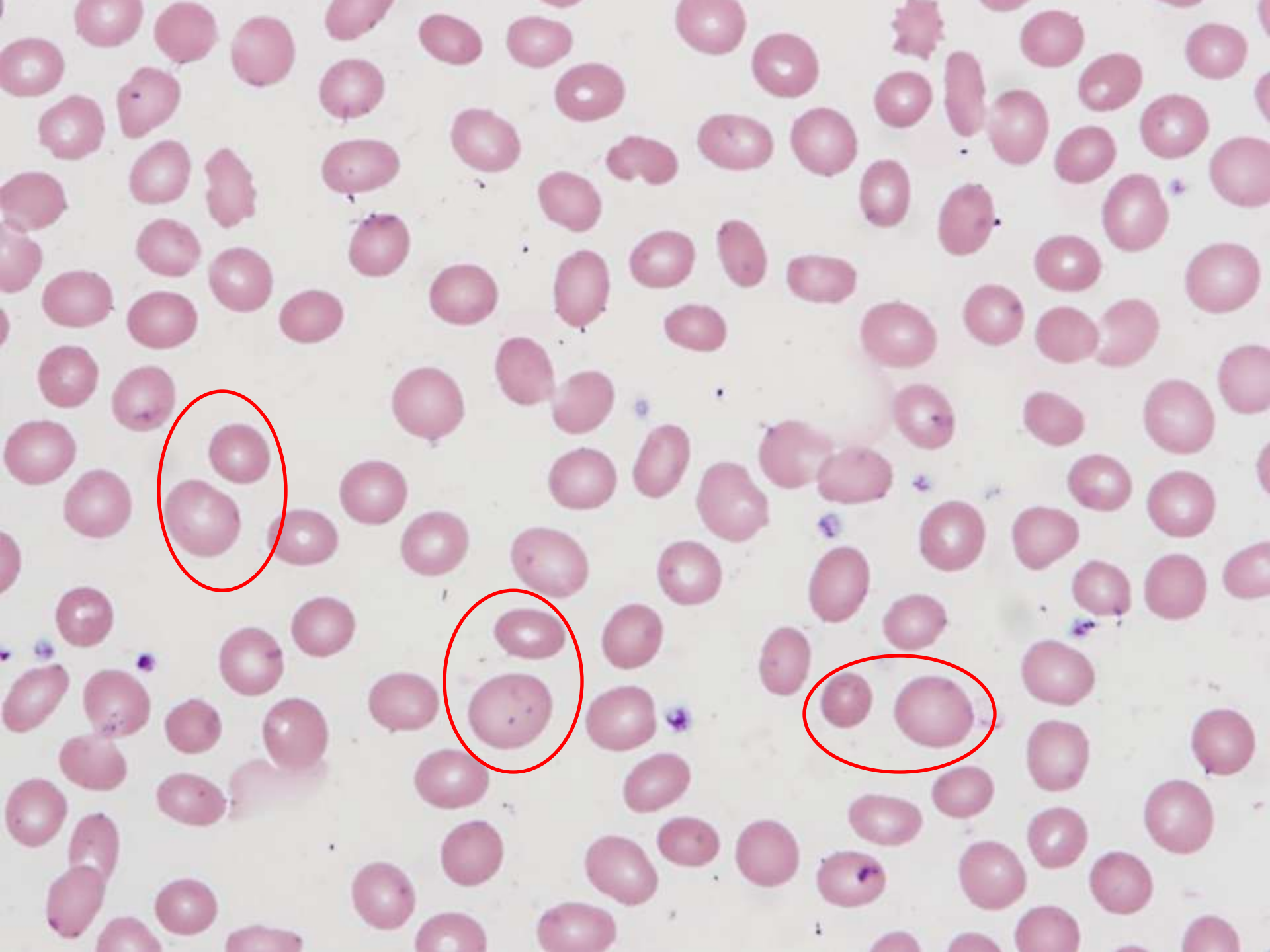
Labs:

- CBC




MCV=98.4 fL , RDW=14.1%

| | |
|---|---|
| Neutrophils | 52% |
| Lymphocytes | 37% |
| Monocytes | 3% |
| Eosinophils | 3% |
| Basophils | 1% |



# Differential diagnosis

Anemia:

- Iron deficiency
- Anemia of chronic disease
- Blood loss
- Vitamin B12 or folic acid deficiency
- Autoimmune hemolytic anemia
- Cold agglutinin disease
- Liver or thyroid disease
- Drugs
- Toxins (alcohol)

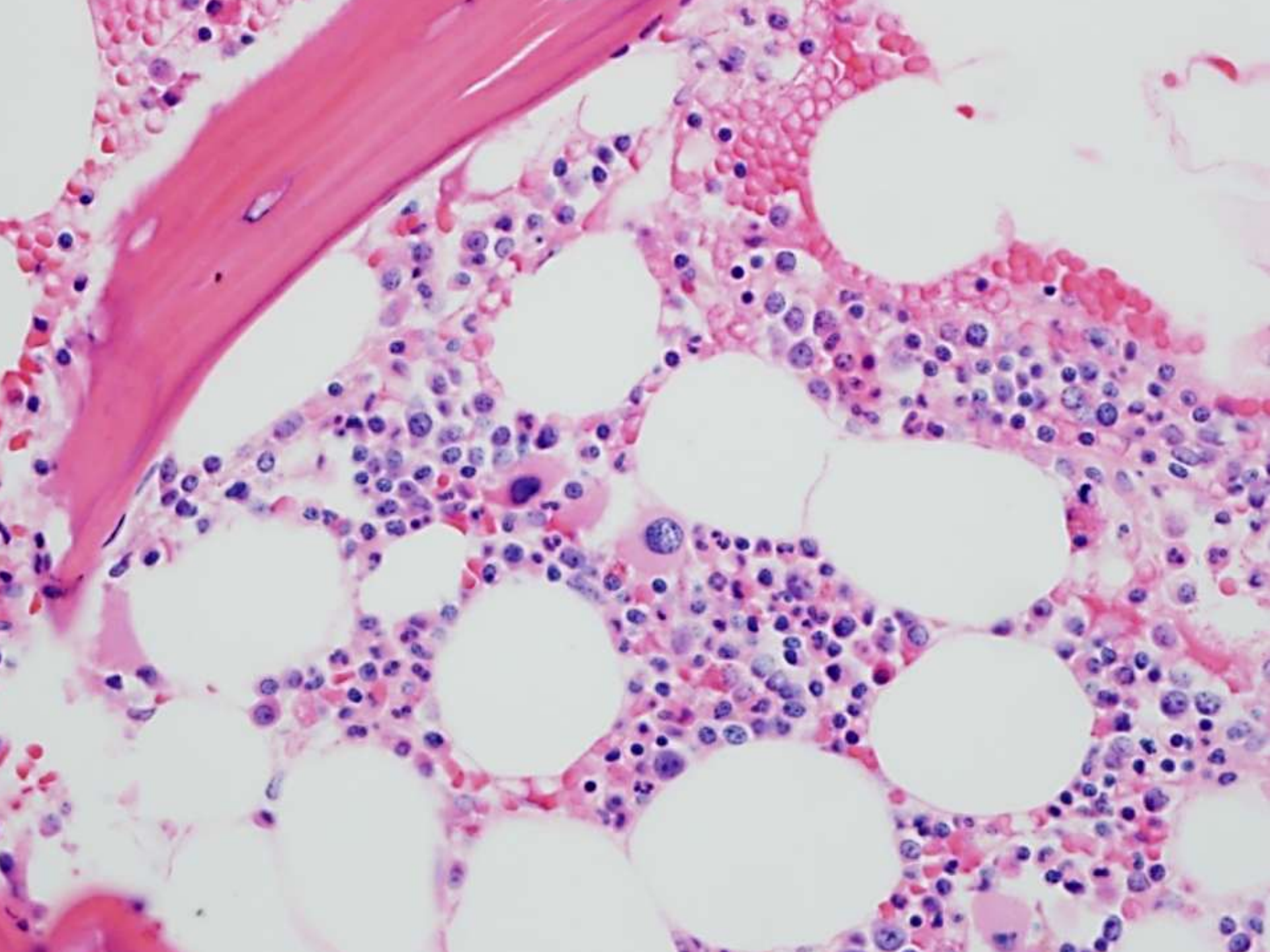
Bone marrow failure:

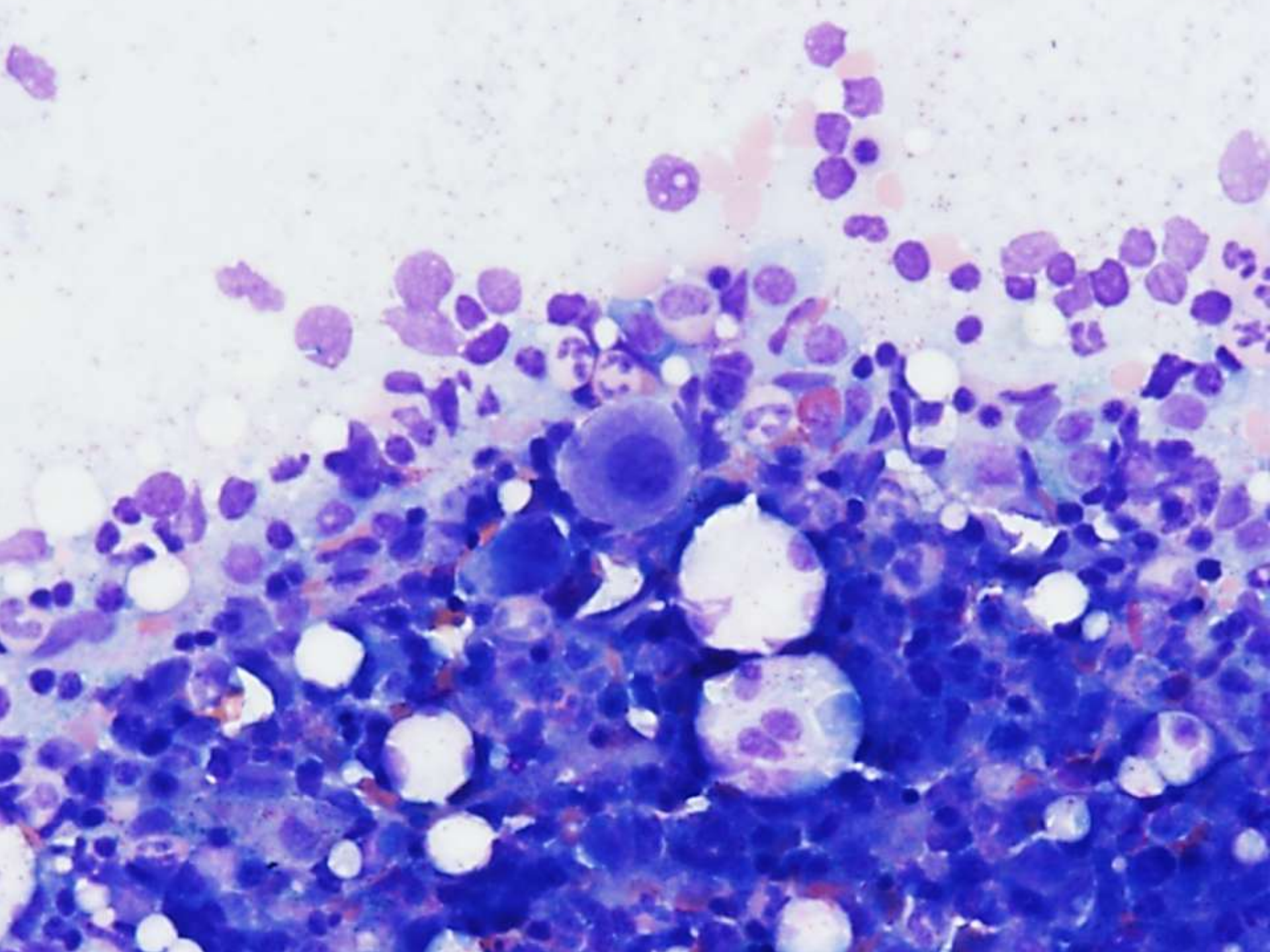
- Aplastic anemia
- Myelodysplastic syndromes

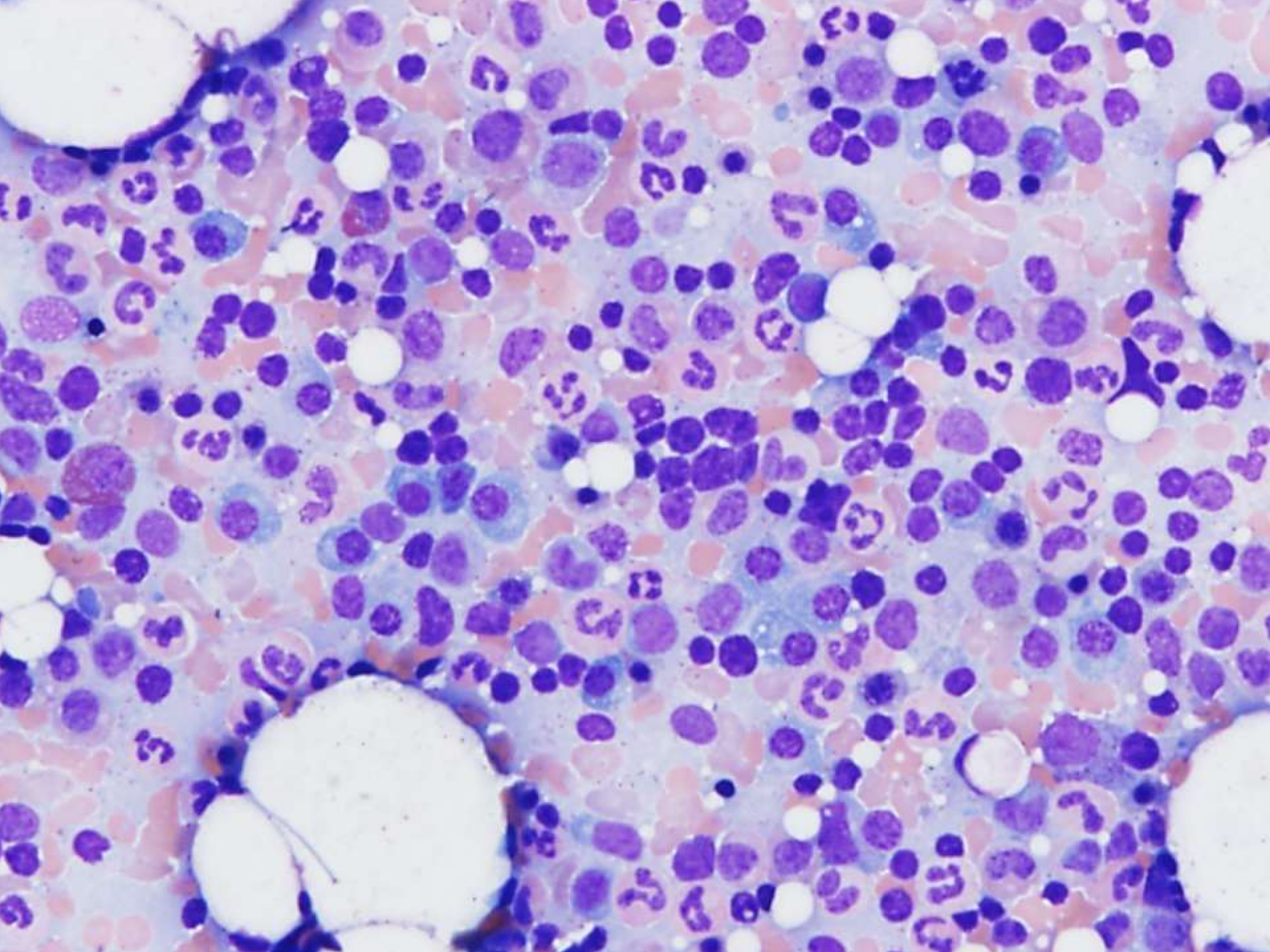
Workup for anemia:

- iron studies,
- LDH,
- haptoglobin,
- B12, folate,
- Coombs test

} within normal limits

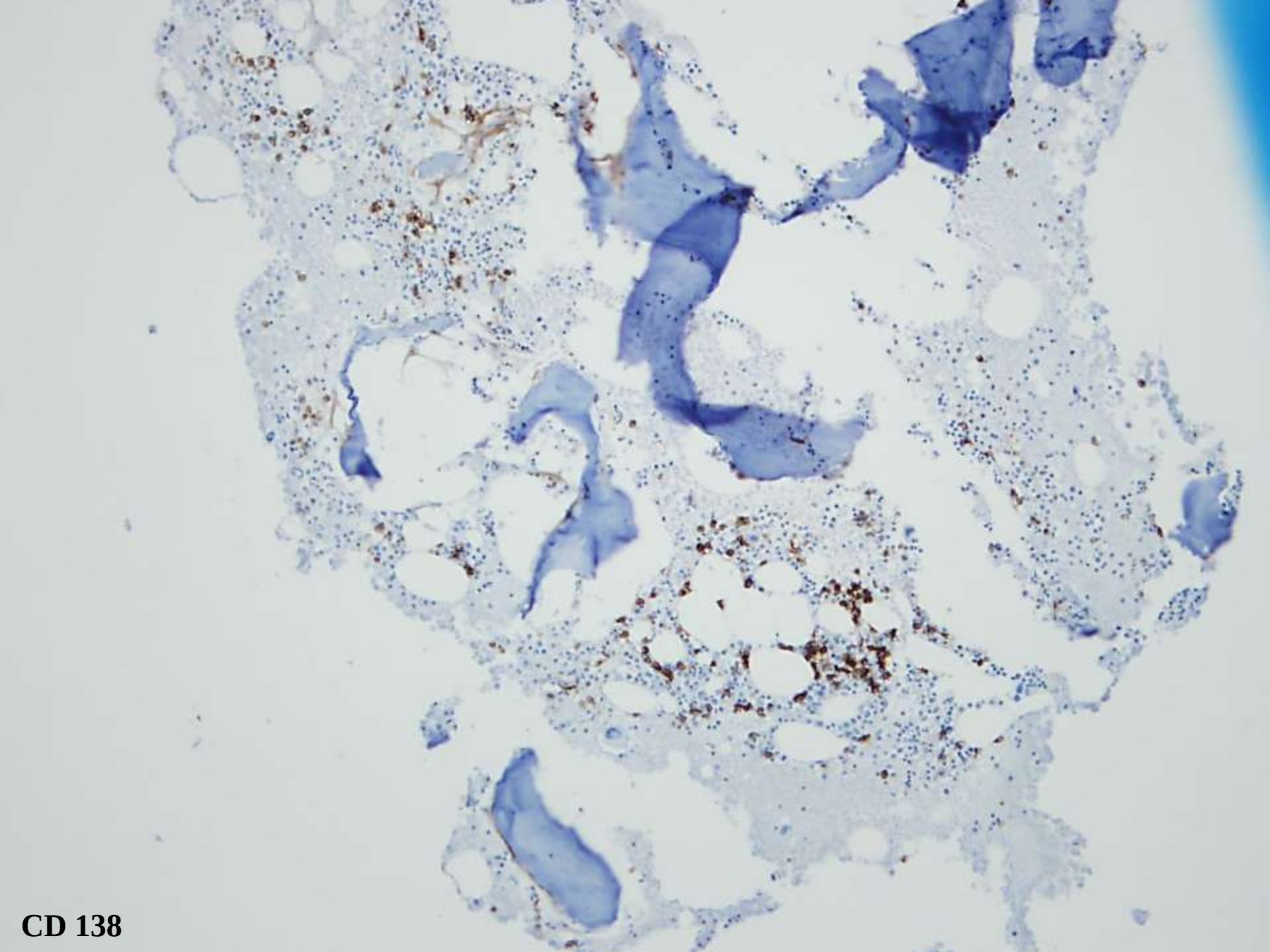






# Bone marrow aspirate

| CELL | RESULT (%) | REFERENCE RANGE |
|---|---|---|
| • Blasts | 0.8 | (0.0 - 2.0) |
| • Promyelocytes | 0.8 L | (2.0 - 8.0) |
| • Other granulocyte precursors | 44.0 L | (50.0 - 70.0) |
| • Erythroid precursors | 36.2 H | (20.0 - 25.0) |
| • Lymphocytes | 7.2 L | (10.0 - 15.0) |
| • Eosinophils | 3.2 H | (1.0 - 3.0) |
| • Basophils | 0.2 | (0.0 - 1.0) |
| • Monocytes | 0.0 | (0.0 - 1.0) |
| • **Plasma cells** | **7.6 H** | **(0.0 - 3.0)** |
| M:E Ratio | 1.3 | (1.2 - 5.0) |



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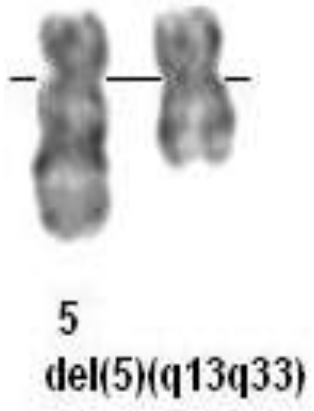
# Additional studies

- Cytogenetic studies:

  46,XX,del(5)(q13q33)[7]/46,XX[13]

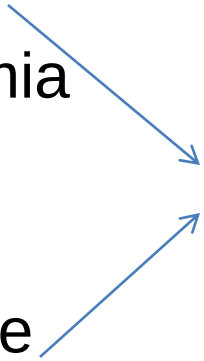



- Flow cytometry:

  a population of kappa light chain restricted plasma cells.

# Summary of findings

- Peripheral blood :
  - -bicytopenia
    - -macrocytic anemia
- Bone marrow:
  - -hypercellular for age
  - -megakaryocytic dysplasia
  - -clonal plasma cells
- Cytogenetics:
  - -isolated del(5) (q13q33)



Inefficient hematopoiesis:
**Myelodysplastic syndrome**

**Plasma cell dyscrasia**

# Differential diagnosis for del(5q)

- **MDS with isolated del(5q)**

  -**older female**
  -**anemia** (usually macrocytic) +/- other cytopenias
  -**thrombocytosis** or normal platelet count
  -**myeloblasts <5%** in BM, **<1%** in PB
  -**absent Auer rods**
  **-isolated del(5q)**

- **Therapy related myeloid neoplasms: t-AML, t-MDS, and t-MDS/MPN**

  -history of **chemotherapy and/or radiotherapy** for neoplastic or non-neoplastic disorders (e.g for Multiple Myeloma)
  -**cytopenias**
  -**dysplastic changes** (usually in all lineages)
  -frequently **complex karytotype**, including **del(5q)**
    -cytogenetic changes:
      ~70% have unbalanced chromosomal aberrations (often of chromosomes **5** and 7), mostly with a complex karyotype
      ~20-30% have balanced chromosomal translocations
    -cases with abnormalities of chromosomes 5 and/or 7 have poor prognosis (median survival <1y)

# Diagnosis

- Myelodysplastic syndrome, best classified as isolated del(5q) in the appropriate clinical context.

- Plasma cell dyscrasia.

# Myelodysplastic syndrome (MDS) with isolated del(5q), also known as “5q- syndrome”

- MDS:
  -clonal disorders of hematopoietic stem cells, characterized by:
  **-inefficient hematopoiesis**,
  -peripheral blood **cytopenias,**
  **-risk of progression** to acute myeloid leukemia (AML).

- MDS del(5q):
  Clinical presentation:
  -predominantly in **women** (7:3)
  -median age of 67
  -symptoms related to anemia

  Peripheral blood:
  -**anemia** (usually macrocytic) +/- other cytopenias
  -normal or increased platelet counts (in 1/3-1/2 cases)
  -absence of circulating blasts (<1%)

# MDS with isolated del(5q)

Bone marrow:

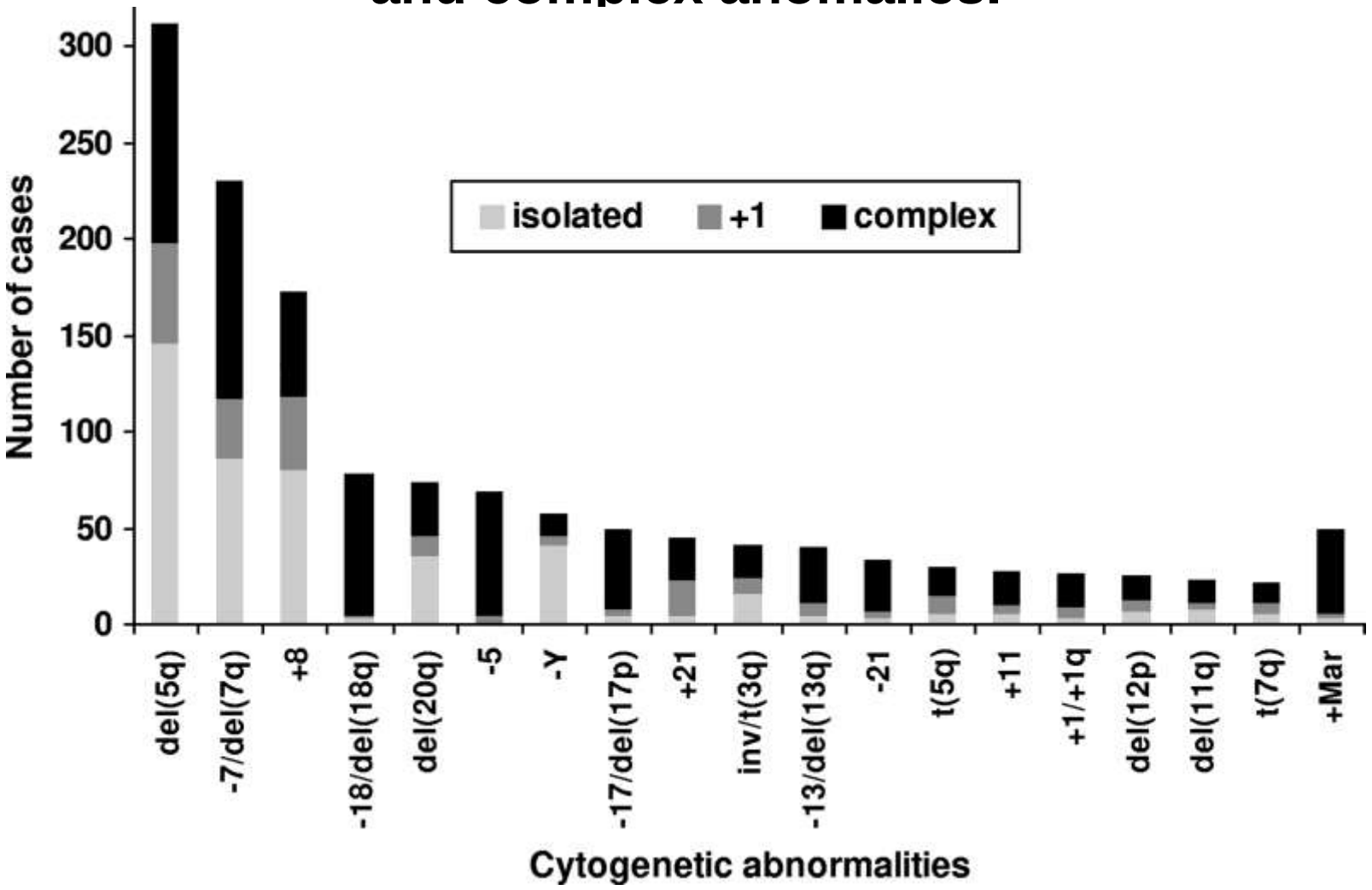
- hypercellular or normocellular
- frequently erythroid hypoplasia
- **megakaryocytes**

  -increased in number

  -**dysplastic:** -normal size /slightly smaller

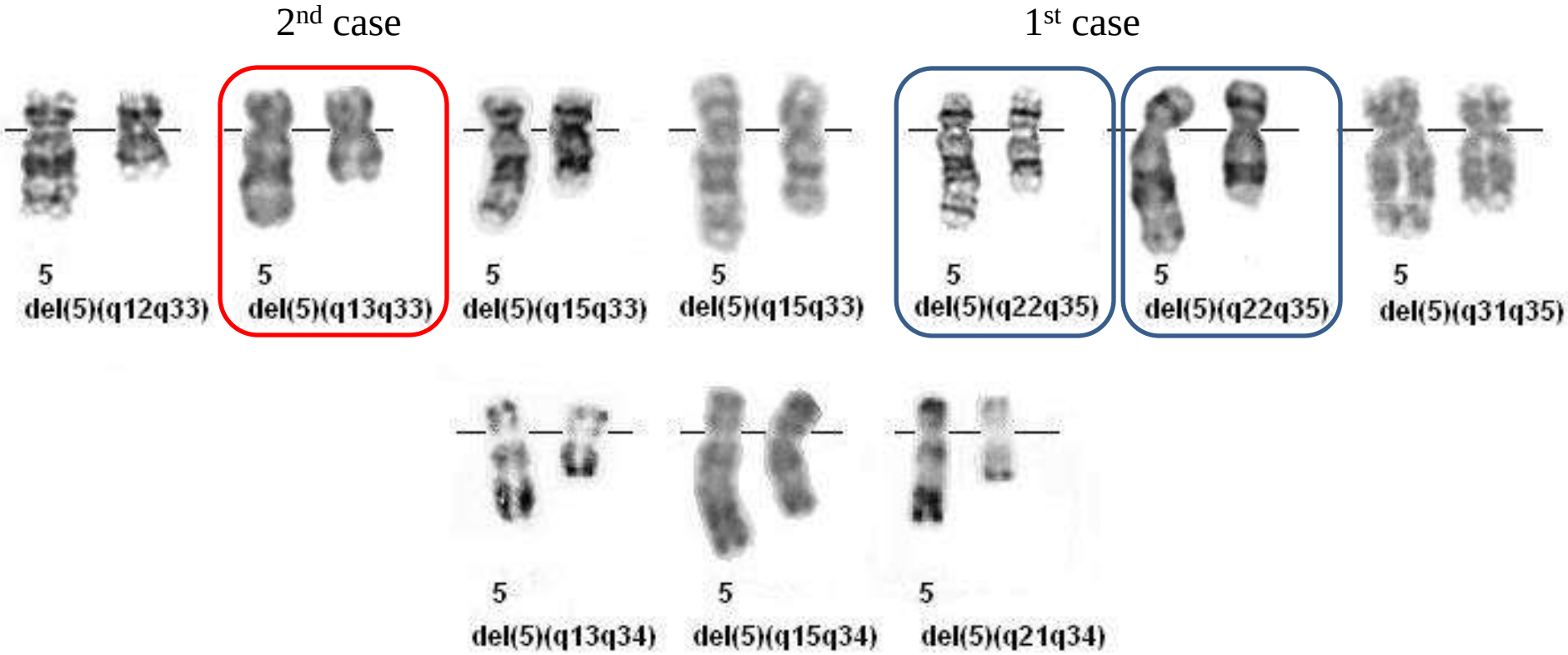
  -non-lobated/hypolobated
- **blasts <5%**
- **absent Auer rods**
- **isolated del(5q)**

# Frequencies of most common cytogenetic anomalies in MDS, subdivided into isolated, with 1 additional anomaly, and complex anomalies.




*Haase D et al. Blood 2007;110:4385-4395*

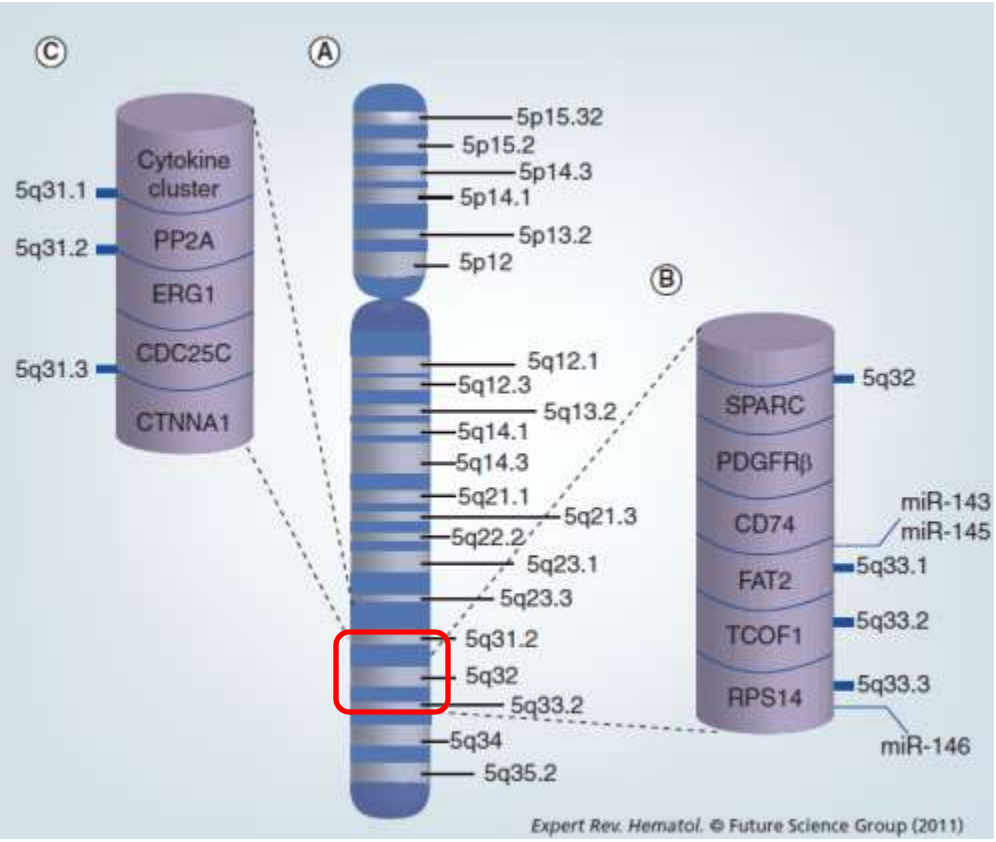
# Isolated del(5q)




-variable size of interstitial deletion

-**q31-q33** invariably deleted

# Molecular pathobiology of MDS del(5q)




- The critical common deleted region (CDR) shared by all patients is approximately 1.5Mb, at 5**q31-q33,** contains tumor suppressor genes
- The lack of mutations of genes mapped in CDR area suggest that **haploinsufficiency** is the basis of 5q-syndrome
- Most studied genes:

  RPS14, miR-145, miR-146, SPARC, ERG1

# Molecular pathogenesis of MDS del(5q)

**RPS14**

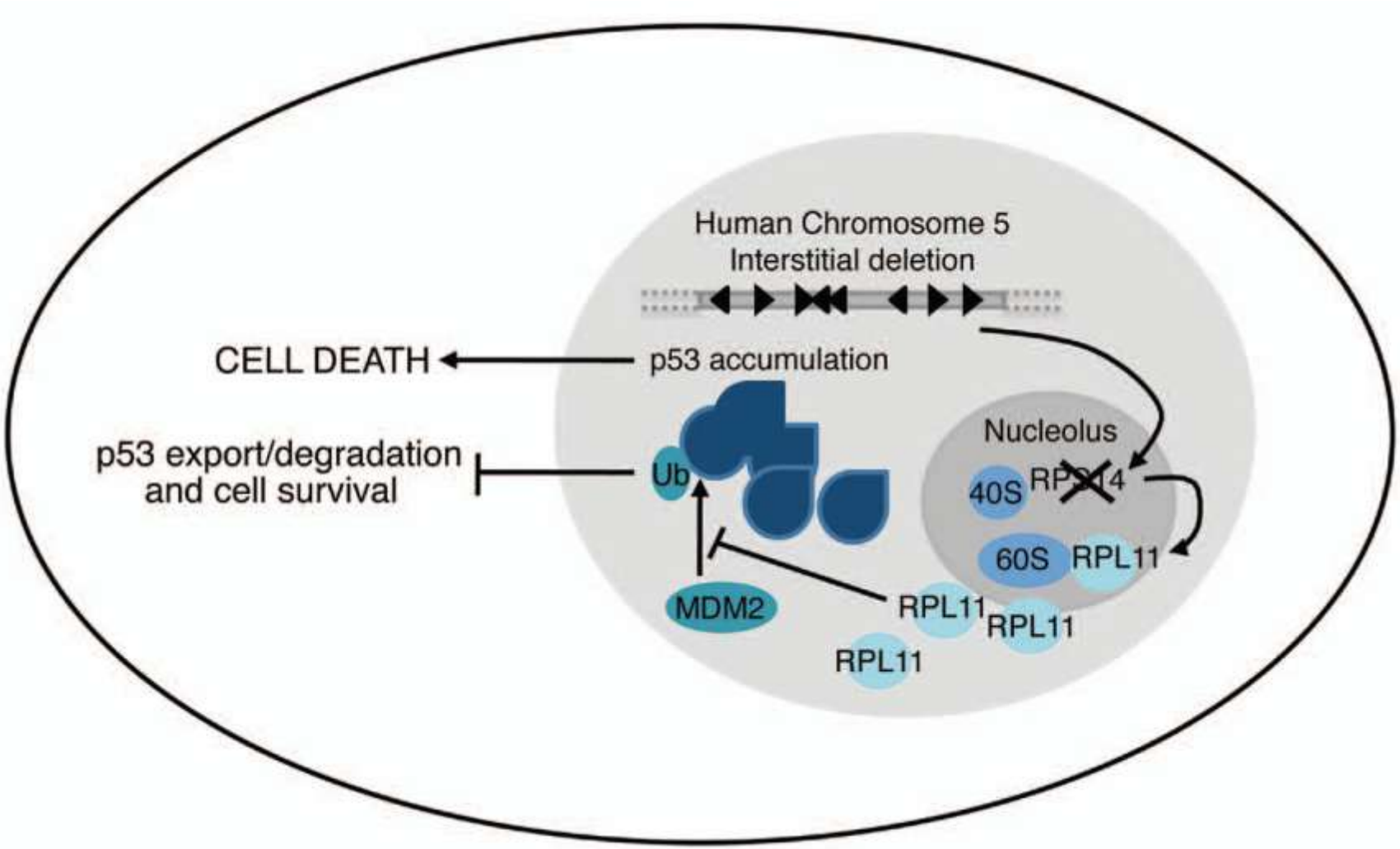
- Encodes the ribosomal protein S14, which is essential for the **assembly of 40S ribosomal** subunits.

- RPS14 haploinsufficiency affects mainly the erythroid line:

  -One hypothesis is that erythroid cells require a large amount of ***globin synthesis*** to produce abundant quantities of hemoglobin. This high level of protein synthesis requires highly efficient ribosome production and activation, which is disrupted by reduced expression of RPS14.

  -An alternative hypothesis: the free ribosomal proteins due to failed ribosomogenesis bind to MDM2, the key regulator of p53 and block MDM2-mediated p53 ubiquitination and degradation. The increased p53 half-life, from minutes to hours, quickly leads to ***higher levels of p53 and increased apoptosis*** of the erythroid elements.

- The knockdown of RPS14 recapitulated the phenotype of the 5q syndrome: a block in erythroid differentiation (leading to erythroid cell apoptosis) with relative preservation of megakaryocyte differentiation.




*A model for a p53-mediated mechanism in 5q- syndrome.*
Haploinsufficiency of **RPS14** induces a block on the MDM2-mediated ubiquitination of p53, leading to p53 upregulation.

*Barlow J.L. Cell Cycle 9:21, 4286-4293; November 1, 2010.*

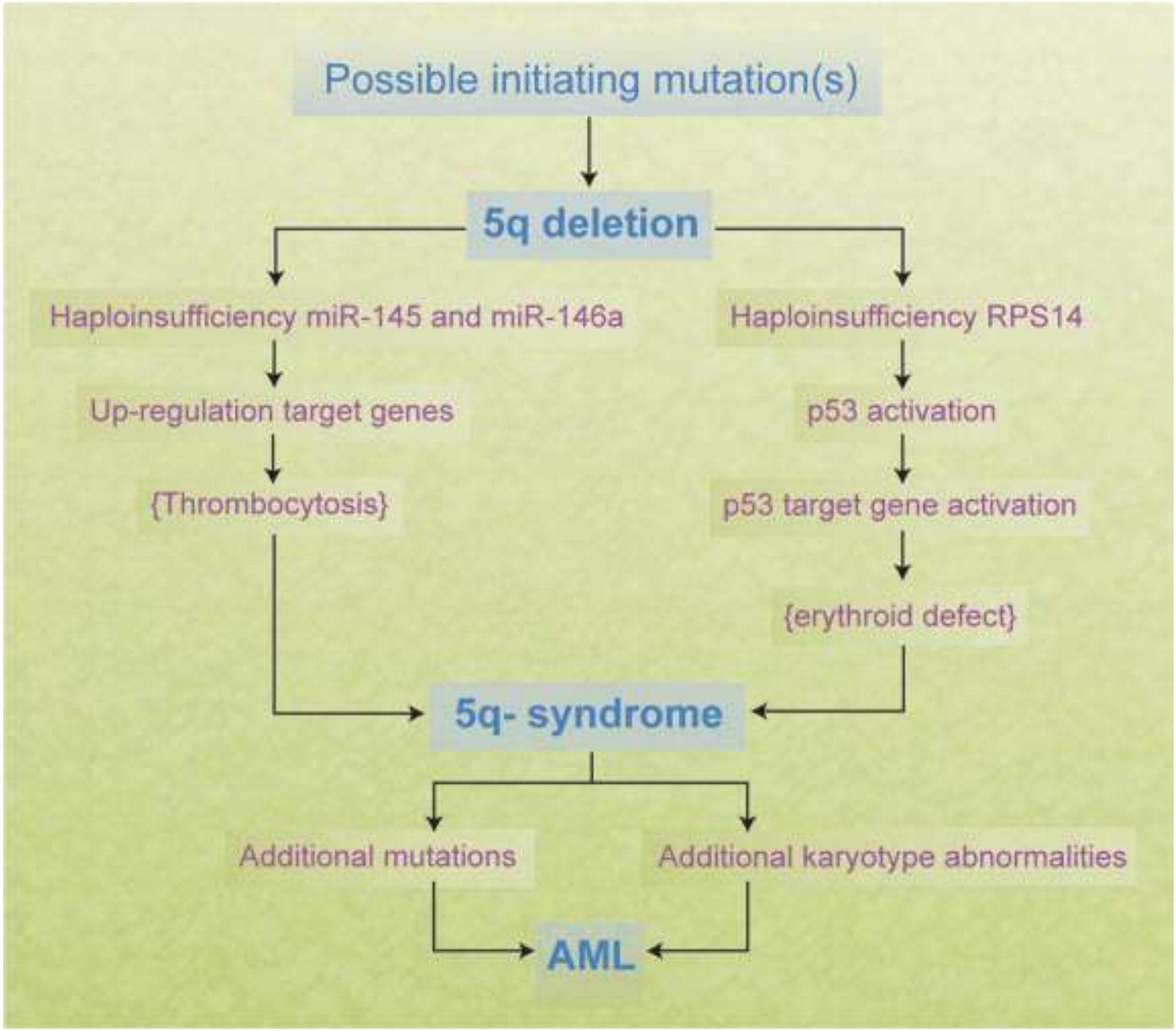
# Molecular pathogenesis of MDS del(5q)

**miR-145** and **miR-146a**

- The microRNAs miR-145 and miR-146a map within the CDR of the 5q syndrome.
- They inhibit the expression of TIRAP and TRAF6, effectors of the innate immune signal.
- Murine models with either microRNA knockdown or TRAF6 overexpression resulted in thrombocytosis and megakaryocytic dysplasia, believed to be IL6 dependent.

**EGR1 (Early Growth Response 1 gene)**

- is a regulator of cyclin D2 and negatively regulates FAS expression
- when one copy of EGR1 there is an increase of **stem-cell self-renewal**.




*Boultwood et al. Blood, 2010 116: 5803-5811*

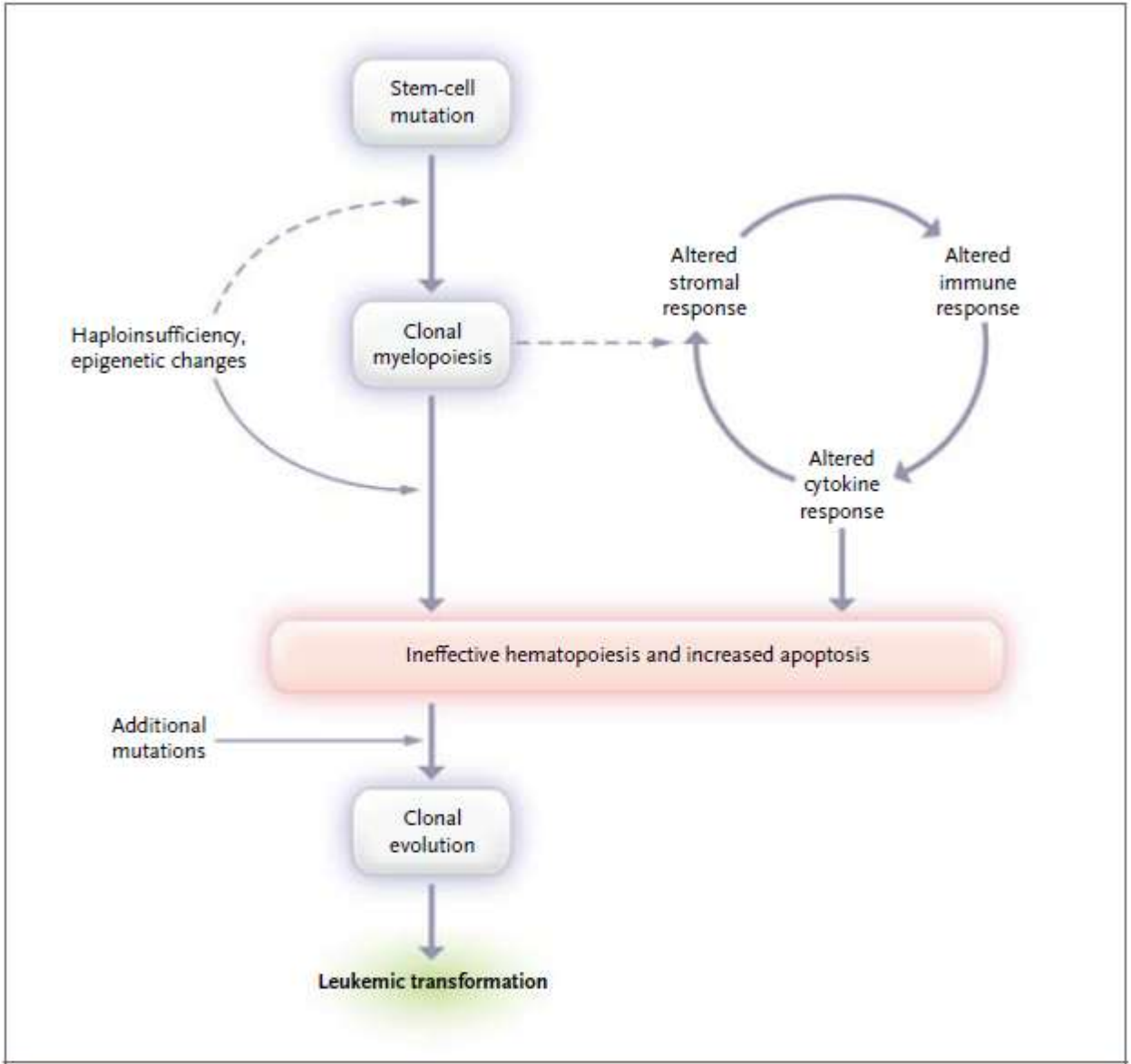


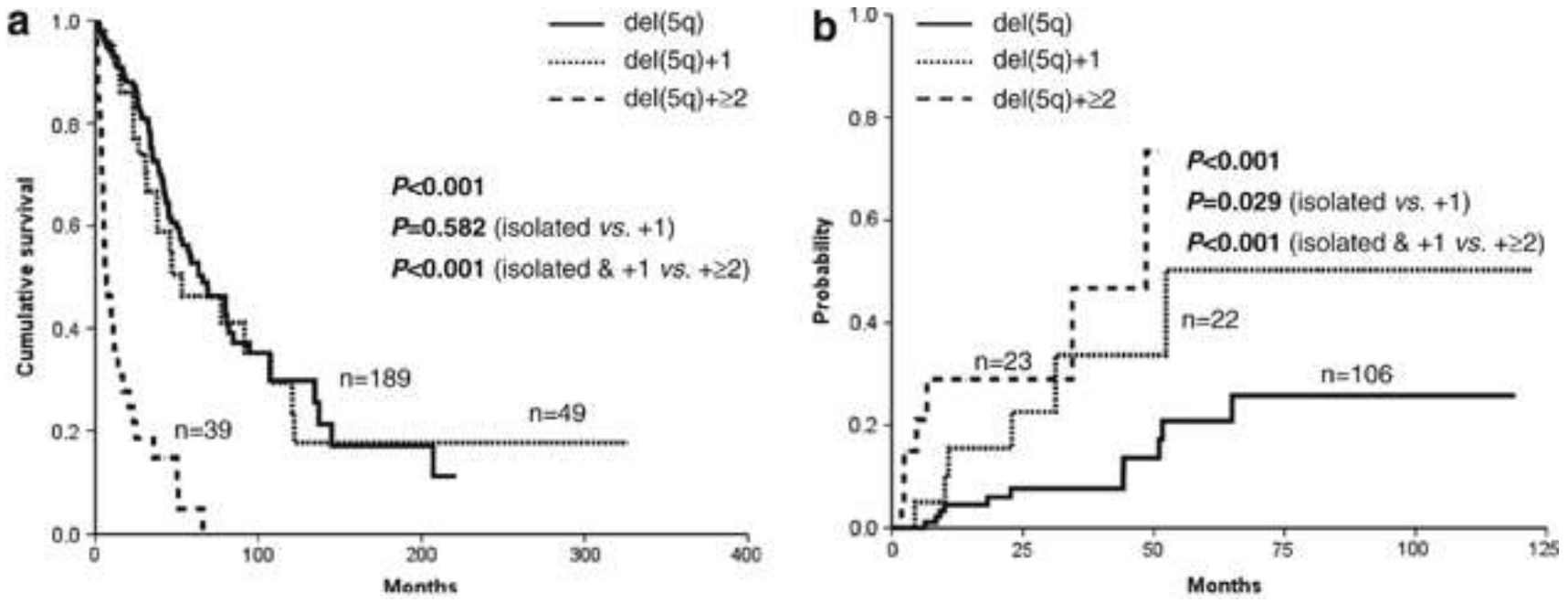

**Figure 3. Putative Pathogenetic Mechanisms and Their Interaction in the Myelodysplastic Syndromes.**
The myelodysplastic syndromes probably arise from a genetically transformed, primitive hematopoietic stem cell. However, subsequent genetic and epigenetic changes contribute to phenotypic diversity, hematopoietic efficiency, and susceptibility to leukemic transformation. Immune, cytokine, and stromal responses in the host also contribute to the disease phenotype.

*Tefferi A.. N Engl J Med 2009;361:1872-85.*

# Prognosis for MDS with isolated del(5q)

- Median survival ~145 months
- Risk of transformation to AML <10%
- Overall better prognosis for MDS with isolated del(5q) compared to MDS with complex abnormalities  in addition to del(5q)

# Prognosis of MDS with isolated del (5q)




Kaplan–Meier curves according to the three defined cytogenetic categories: isolated del(5q), del(5q)+**1**, del(5q)+**2** in MDS patients with <5% blasts in bone marrow (BM).

(a) Actuarial probability of **overall survival** **b)** Cumulative **probability of AML transformation**

*Mallo M. Leukemia (2008) 22, 1874–1881.*

# Treatment-Lenalidomide

- Lenalidomide is an analog of thalidomide that is approved by the FDA for the treatment of patients with transfusion dependent anemia due to **low-** or **intermediate risk** MDS associated **with a deletion 5q** with or without additional cytogenetic abnormalities."

- Although nearly half of patients with low-risk MDS reduce their need for transfusions after lenalidomide therapy, those with **5q- MDS often have complete cytogenetic remissions**.

- The molecular targets of lenalidomide have been investigated by studying its in vitro effects on growth, maturation, and global gene expression in differentiating erythroblasts from patients with MDS with del(5).

  *Deletion of some 5q genes sensitize the cells to therapeutic agents. Lenalidomide inhibited growth of del(5q) erythroblasts but did not affect normal cells.

  *Has antineoplastic, antiangiogenic, antiadhesive, and immunomodulatory properties.

  *Up-regulation of the tumor suppressor gene ***SPARC*** , located at 5q32 within the CDR of the 5q syndrome. The principal function of SPARC is the regulation of extracellular matrix interactions. SPARC has antiproliferative, anti-adhesive, and anti-angiogenic properties, all recognized effects of immunomodulatory drugs.

  *Two cell cycle–regulating phosphatases encoded by the genes on 5q, ***CDC25C*** and ***PP2A***, have been implicated in the favorable response to lenalidomide.

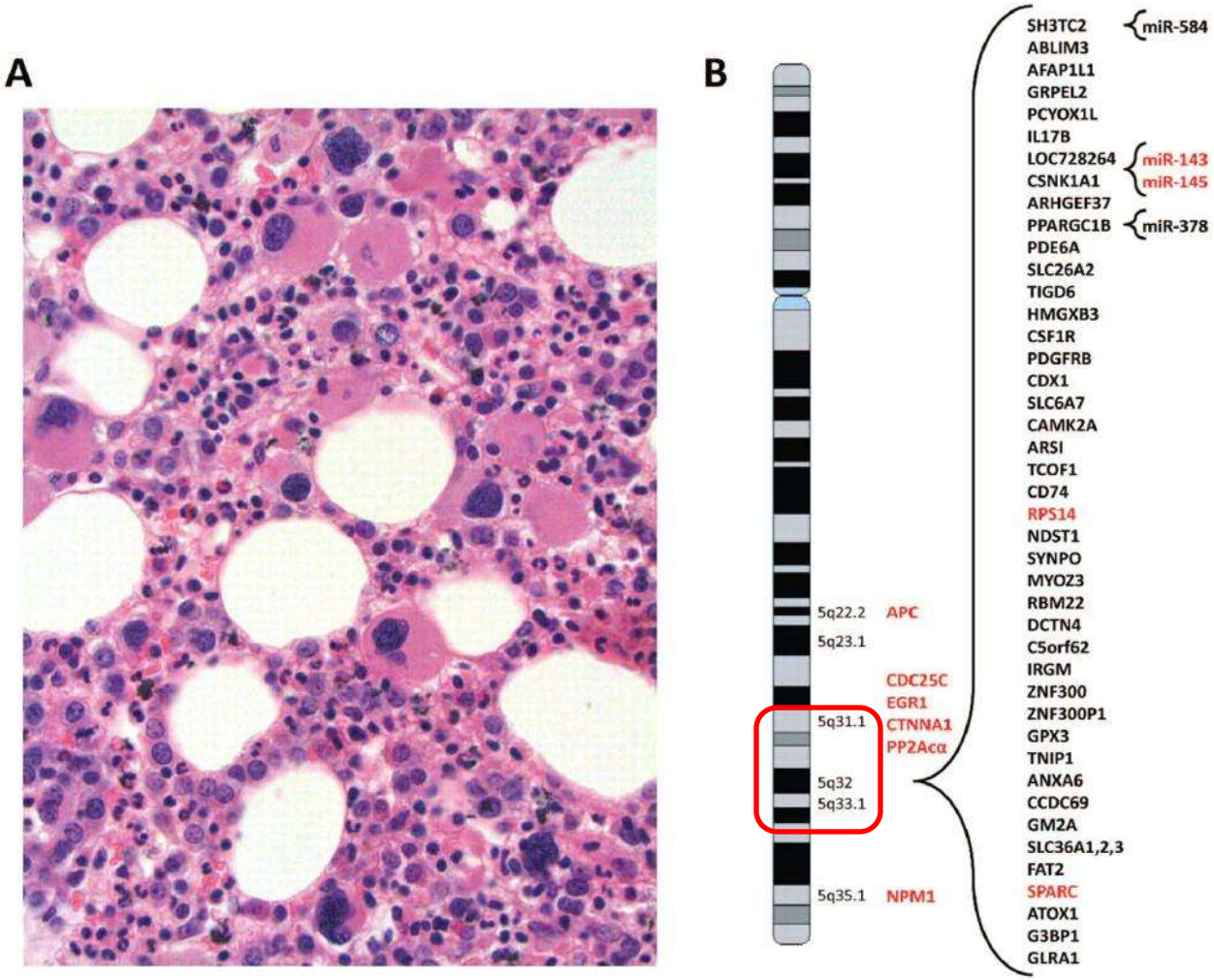
- Lenalidomide is also used for treatment of relapsed or refractory multiple myeloma

# Summary

Diagnosis of MDS with isolated del(5q) requires integration of clinical, hematologic, morphologic and genetic findings.

- Clinical:
  - **-older female** (7:3 female to male ratio)
  - **-no hx of chemotherapy /radiotherapy**
- Peripheral blood:
  - **-macrocytic anemia**
  - -normal/high platelet counts
- Hallmark bone marrow features of MDS del(5q):
  - -erythroid hypoplasia
  - -**megakaryocytic dysplasia** (small, mono-/ hypo-lobated nuclei)
  - -less than 5% myeloblasts
  - -**isolated del(5q)**
- Prognosis:
  - -low risk of progression to leukemia
  - -good prognosis
- Treatment:
  - -lenalidomide

# MDS with isolated del(5q)




**Characteristic bone marrow morphology in MDS with isolated del(5q) showing numerous hypolobulated megakaryocytes**

haematologica
the hematology journal

*Jadersten, M. et al. Haematologica 2011;96:177-180*

# Thank you

- Dr. Lauren Smith

# References


1)Boultwood J, Pellagatti A, McKenzie A.N.J. and Wainscoat J.S. Advances in the 5q- syndrome. *Blood 2010 116: 5803-5811*.

2) Barlow J.L. New insights into 5q- syndrome as a ribosomopathy. *Cell Cycle 2010 9:21, 4286-4293.*

3) Swerdlow S.H., Campo E., Harris N.L., Jaffe E.S., Pileri S.A., Stein H., Thiele J., Wardiman J.W. (Eds): WHO Calssification of Tumours of Haematopoietic and Lymphoid Tissues. IARC: Lyon 2008.

4) Haase et al. Blood 2007;110:4385-4395.

5) Mallo M. Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia (2008) 22, 1874–1881.

6) Tefferi A. Mechanisms of disease. Myelodysplastic syndromes. N Engl J Med 2009;361:1872-85.

7) Padron E. Biology and treatment of the 5q- syndrome. Expert Rev. Hematol. 2011 4(1), 61–69

# The International Prognostic Scoring System for (MDS)

| Prognostic variable | Score | Cytogenetic abnormalities (frequency in primary MDS) |
|---|---|---|
| Poor-risk karyotype | 1.0 | -complex (~18%)<br>-monosomy 7/ del(7q) (~2%)<br>-other chromosome 7 abnormalities (<1%) |
| Intermediate-risk | 0.5 | -sole trisomy 8 (~4%)<br>-others not included in poor or good-risk categories ***(<1% each) |
| Good-risk karyotype | 0 | -normal<br>-sole del(5q) (6%)<br>-sole del(20q) (~3%)<br>-sole –Y (~2%) |

***Two abnormalities not including chromosome 7, del(12p), inv(3)/t(3;3), -17/del(17p13), i(17q), del(11q23), +21, +19, +11, +15 etc.