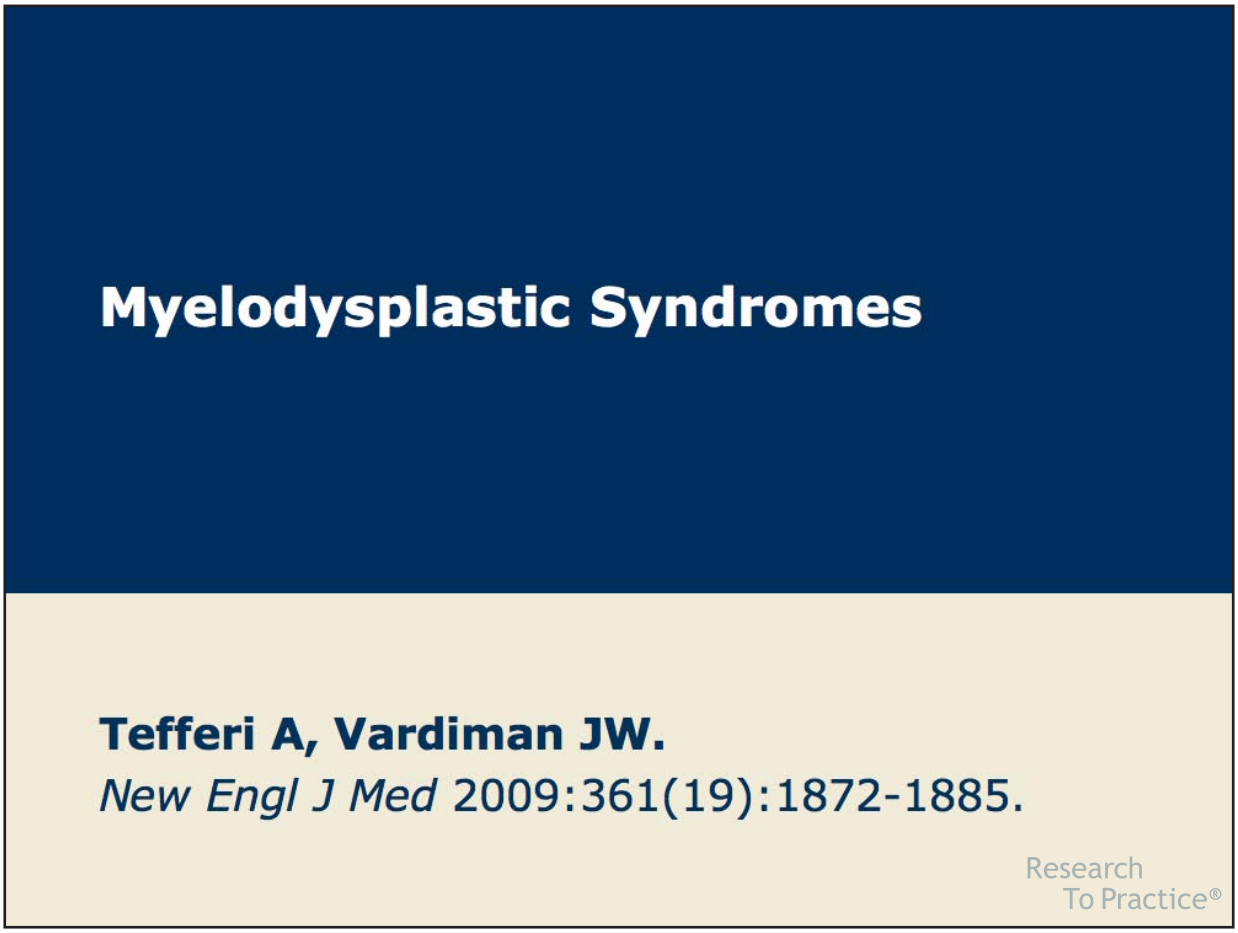
# Myelodysplastic Syndromes

## Presentation discussed in this issue:

Tefferi A, Vardiman JW. **Myelodysplastic syndromes.** *N Engl J Med* 2009;361(19):1872-85. **Abstract**

## Slides from journal article



# Introduction

- According to the 2008 World Health Organization (WHO) classification system for hematologic cancers, primary myelodysplastic syndromes are one of the five major categories of myeloid neoplasms (*Blood* 2009;114:937).
- The main feature of myeloid neoplasms is stem-cell-derived clonal myelopoiesis with altered proliferation and differentiation.
- Increasing evidence exists that the following contribute towards the development of myelodysplastic syndromes:
  - Haploinsufficiency
  - Epigenetic changes
  - Cytokine, immune system and bone marrow stroma abnormalities

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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# Classification of Myeloid Neoplasms According to WHO Criteria

- Acute myeloid leukemia and related neoplasms, including therapy-related myelodysplastic syndromes
- Myelodysplastic syndromes
  - Refractory cytopenia with unilineage dysplasia (RCUD)
    - Refractory anemia
    - Refractory neutropenia
    - Refractory thrombocytopenia
  - Refractory anemia with ring sideroblasts (dysplasia limited to erythroid lineage and ring sideroblasts ≥15% of bone marrow [BM] erythroid precursors)
  - Refractory cytopenia with multilineage dysplasia (RCMD)

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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# Classification of Myeloid Neoplasms According to WHO Criteria (continued)

- Myelodysplastic syndromes (continued)
  - Refractory anemia with excess of blasts (RAEB)
    - RAEB-1 (2-4% circulating blasts or 5-9% marrow blasts)
    - RAEB-2 (5-19% circulating blasts or 10-19% marrow blasts or Auer rods present)
  - Myelodysplastic syndrome (MDS) with isolated del(5q)
  - MDS (unclassifiable)
- Myeloproliferative neoplasm
- Myelodysplastic - myeloproliferative neoplasms
- Molecularly characterized myeloid or lymphoid neoplasms associated with eosinophilia.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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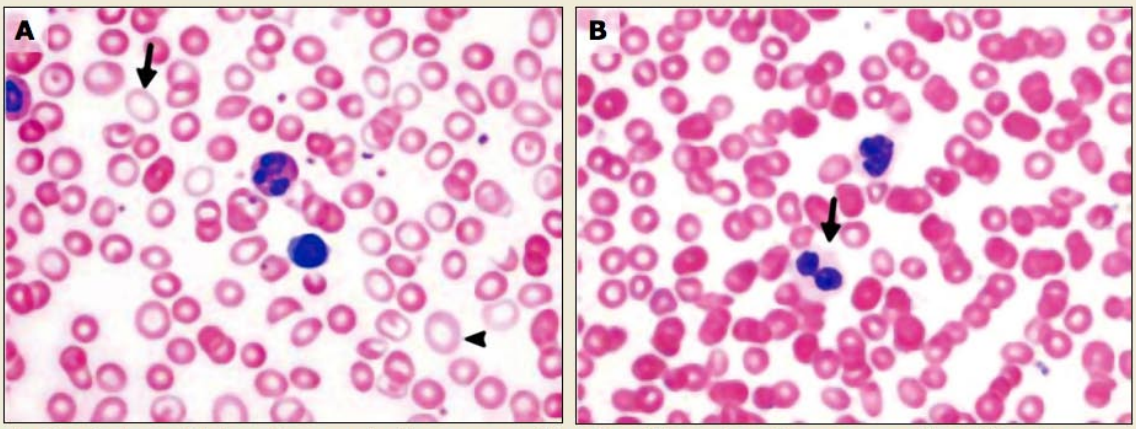
# Morphologic Features of Peripheral Blood and Bone Marrow in Myelodysplastic Syndromes




**A. Peripheral blood sample from a patient with refractory anemia with ring sideroblasts, with dimorphic red cells; some cells are hypochromic (arrow). Anisocytosis with occasional macroovalocytes is noted (arrowhead)**
**B. Peripheral blood sample from a patient with RAEB, demonstrating pseudo-Pelger-Hüet cells with hypercondensed chromatin, hypolobulated nuclei and virtually colorless cytoplasm (arrow).**

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.



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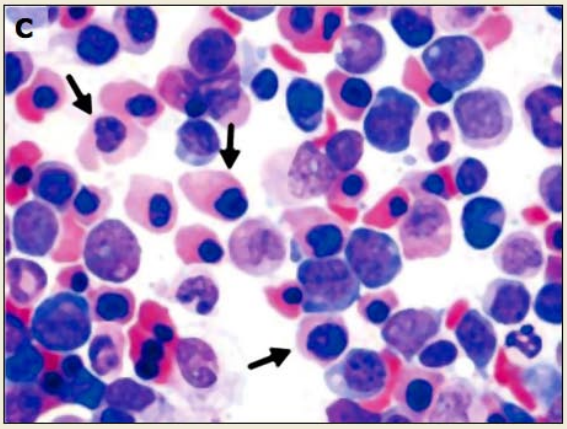
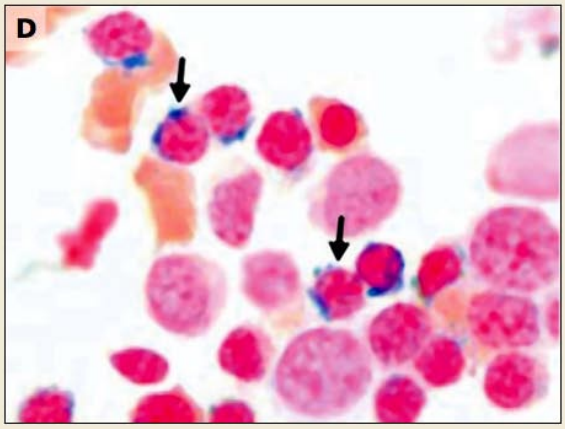
# Morphologic Features of Peripheral Blood and Bone Marrow in Myelodysplastic Syndromes




**C. Dyserythropoiesis (arrows) in a BM sample obtained from a patient with refractory cytopenia with multilineage dysplasia.**
**D. Ring sideroblasts (arrows) from a patient with refractory anemia. Ring sideroblasts are characterized by at least five granules of iron that encircle the nucleus of the erythroid precursor.**

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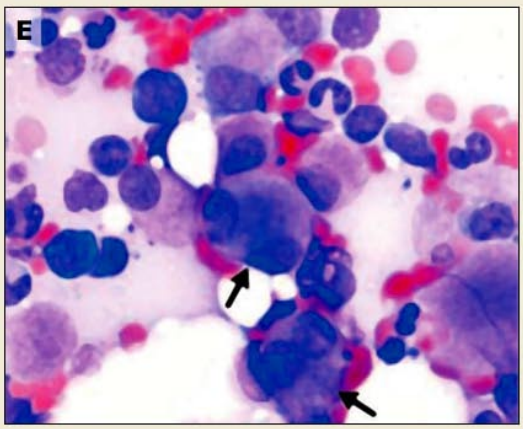


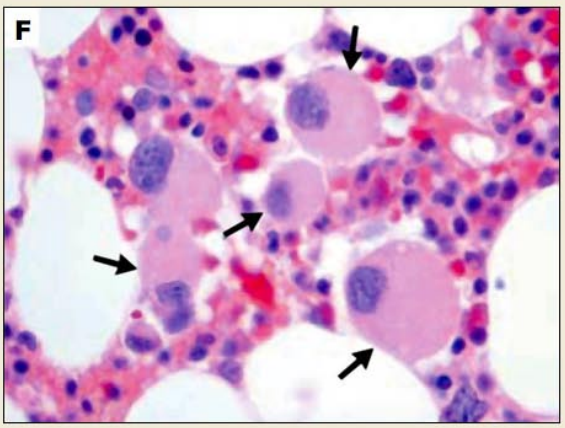


**E. Dysplastic small megakaryocytes (arrows) with monolobed or bilobed nuclei and mature granular cytoplasm in the aspirate smear of a patient with RAEB.**
**F. BM tissue section of a patient with MDS and isolated del(5q). The megakaryocytes are of medium size, with hypolobulated nuclei (arrows).**

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.


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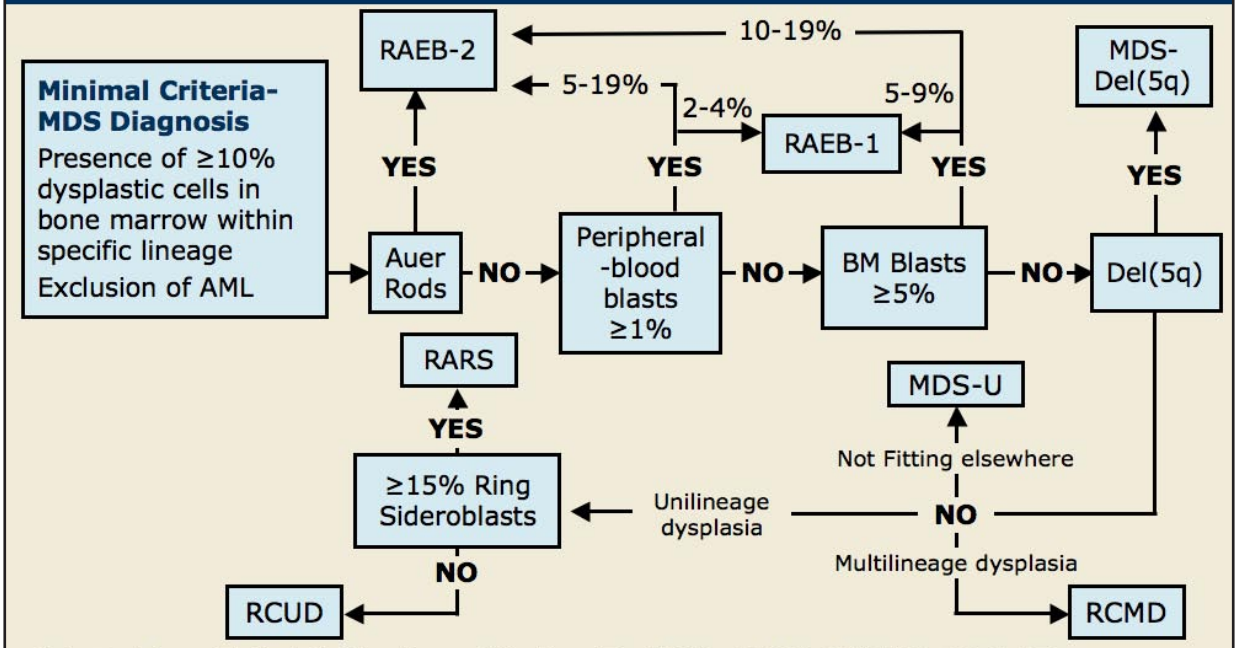
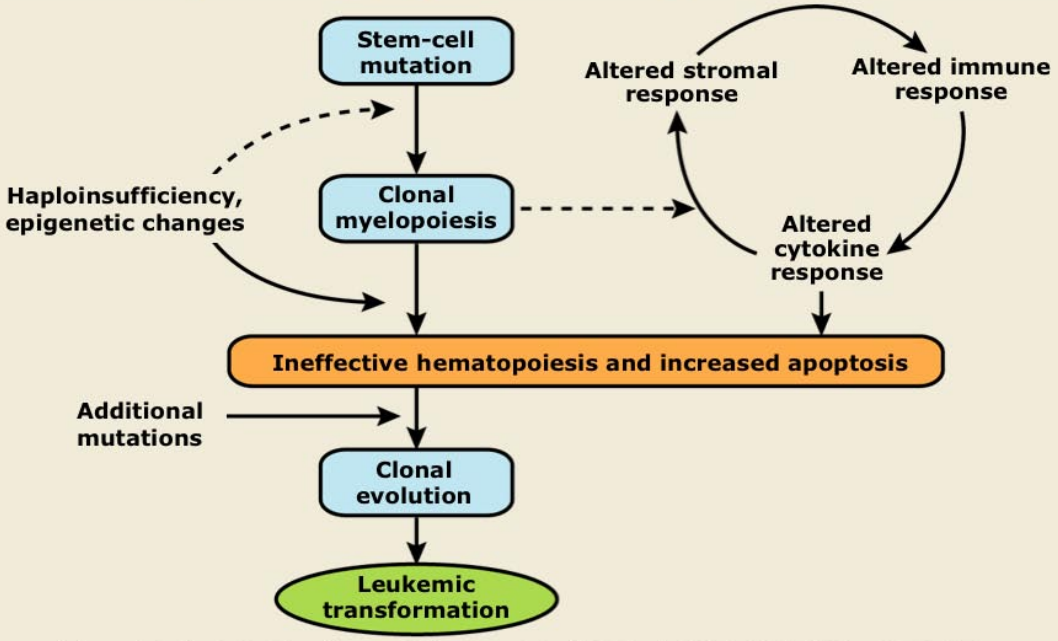
# Classification Algorithm of Adult-Onset Primary MDS




Adapted from Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

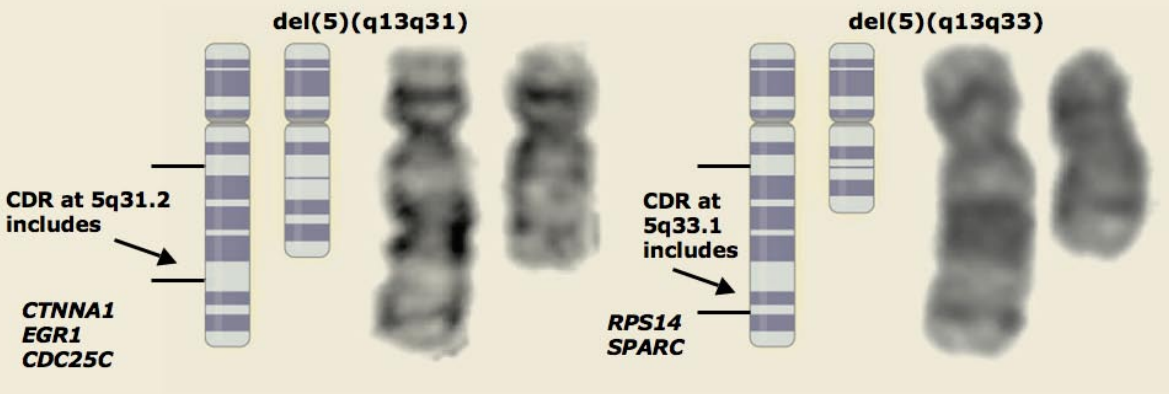


# Putative Pathogenic Mechanisms and Their Interaction in the Myelodysplastic Syndromes




Adapted from Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

# Ideograms and Commonly Deleted Regions Involving Del(5q)




**In typical 5q minus syndrome, the commonly deleted region (CDR) has been mapped to 5q33.1 (at right), which contains the genes for osteonectin (*SPARC*) and ribosomal protein S14 (*RPS14*).**
**In the del(5q)-associated myelodysplastic syndrome—acute myeloid leukemia, the commonly deleted region has been mapped to 5q31.2 (at left), which contains the genes for catenin alpha 1 (*CTNNA1*), early growth response 1 (*EGR1*) and cell division cycle 25 homologue C (*CDC25C*).**

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.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# Treatment Options

- Allogeneic hematopoietic stem-cell transplantation (AHCT)
  - The only treatment able to induce long-term remission in patients with MDS is AHCT, though it is not applicable to most patients because the median age of diagnosis is greater than 70 years and it is only recommended for patients with advanced stage disease.
  - Stem cell transplantation is associated with:
    - High rate of treatment-related death (39% at 1 year)
    - Suboptimal disease-free survival (29% at 5 years)
    - Chronic graft-versus-host disease (15% at 1 year)

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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# Treatment Options (continued)

- Demethylating agents (azacitidine, decitabine) or low-dose cytarabine
  - Increased remission rates with these drugs versus supportive care
  - Complete remission rates achieved with azacitidine or decitabine (9%-17%) are similar to the rates obtained with low-dose cytarabine (11-18%).
    - Complete remission rates are lower than rates obtained with induction chemotherapy in patients with acute myeloid leukemia (>50%).
  - Use of these drugs may delay blastic transformation.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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# Treatment Options (continued)

- Lenalidomide
  - Lenalidomide can reduce the need for transfusion in about two-thirds of patients and can induce complete cytogenetic responses in almost half of the patients with low- or intermediate-1-risk MDS associated with del(5q).
  - The drug's effect is less on variants of MDS disease with karyotypes other than del(5q).
- Other drugs/treatment options
  - Erythropoiesis stimulating agents help anemic patients with low-risk disease and a serum erythropoietin level less than 200 mIU/mL.
  - Granulocyte stimulating growth factors are only cost-effective in patients with neutropenia and fever or overt infection.
  - Many patients can be treated effectively with red cell transfusion alone.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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# Conclusions

- Myelodysplastic syndromes appear to constitute several molecularly distinct entities that share common changes in blood and BM.
  - This heterogeneity poses a challenge for the creation of a unifying framework into which information about the molecular and biologic mechanisms of myelodysplastic syndromes can be incorporated.
- From a treatment standpoint, understanding the mechanisms of ineffective hematopoiesis and leukemic transformation may be as important as understanding the primary oncogenic events.
- Increasing information on the identity and nature of transformed hematopoietic stem cells and advances in biotechnology will help to better understand this disease.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.