Myelodysplastic Syndromes

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Primary Objectives

- To review clinical presentation of MDS and differential diagnosis
- To review the epidemiology and diagnostic evaluation of patients with MDS
- To review insights into the pathogenesis of MDS
- To review treatment recommendations for patients with low and high risk MDS
- To discuss special cases: hypoplastic MDS, MDS with 5q deletion, MDS with Ringed Sideroblasts, ICUS/CHIP

Case

- 71 year old female with fatigue and neuropathy is referred to OSU for second opinion and concern for a marrow disorder.
- WBC 1.8 (10% segs), Hg 8.3g/dL, Plt 277
  - Bone marrow biopsy with dyserythropoiesis and dysmegakaryopoiesis, low blasts
  - Normal female karyotype

Case continued

- Exam findings:
  - Dentures in place
  - Severe sensory and motor neuropathy

Case continued

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  - Dentures in place
  - Severe sensory and motor neuropathy
- She mentioned that she had recently seen on ABC news a report of Zinc toxicity from Poligrip.
  - She stopped using the product about a month prior, but had used it for 4-5 years.

Case continued

- Her Zinc level was high at 2800ug/L in the urine with Zn/Cr ratio of 5456/ug/g creat (nl 100-900)
- Serum copper level is undetectable

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- Serum copper level is undetectable
- Copper replacement given, CBC normal within 3 weeks.

Differential Diagnosis: Non-Hematologic Causes of Cytopenia

- Reactive/Temporary Cause
  - Drug Effects
  - Infection (viral, bacterial, etc.)
- Nutritional Deficiencies
  - B12, folate, copper, iron
  - Alcoholism, liver dysfunction
- Autoimmune Disorders
  - Hypothyroidism
  - Rheumatologic Disorders

Case 2

- 63-year-old woman with no PMH presents to her internist for her first evaluation in 5 years to re-establish care.
  - She reported worsening fatigue worsening for about a year
  - Mild shortness of breath with activity
  - Occasional bruising but usually after an injury
- Exam: Notable for pallor, mild systolic murmur, and scattered small bruises

Laboratory Results:

Hgb	9.2g/dL
MCV	101
WBC	2.3
ANC	690/uL
Blasts	None
Platelet	64,000/uL

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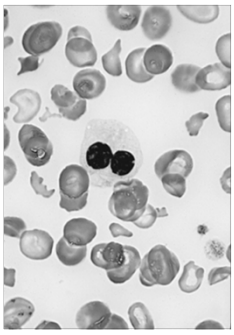
Blasts	None
Platelet	64,000/uL
B12	810
Folate	20
Erythropoietin	254 (normal 2-20)

Diagnostic Work-Up

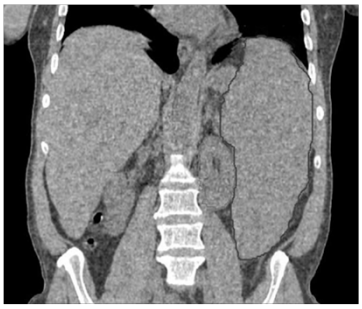
- Peripheral blood smear
- B12, folate, iron studies, copper level
- LDH, haptoglobin, DAT, retic count, epo level
- TSH
- HIV, Hepatitis B and C, and Parvovirus B19
- SPEP, PNH
- If symptomatic, possibly CT abdomen or ultrasound spleen
- Bone marrow biopsy including cytogenetics
- Hematologic neoplasm sequencing panel

Peripheral Smear



https://en.wikipedia.org/wiki/Myelodysplastic_syndrome#/media/File:Hypogranular_neutrophil_with_a_pseudo-Pelger-Huet_nucleus_in_MDS.jpg

Imaging



https://upload.wikimedia.org/wikipedia/commons/8/89/Tumor_Myelodysplastic_Spleen.JPG

Case continued

- Bone marrow biopsy returns consistent with MDS with 8% blasts.
- Cytogenetics show a complex karyotype with trisomy 8, deletion 7, and deletion of 20q
- Sequencing panel reveals mutations of ASXL1 and TET2

Epidemiology

- SEER officially began to track in 2001
  - 15,000 new diagnoses per year
  - Median age at presentation is 70
  - Incidence increases with age
    - < 40 years 0.14 per 100,000
    - ≥ 80 years 36 per 100,000
  - Male predominance

Epidemiology

- **Risk factors**
  - **Age**
  - **Prior chemotherapy**
    - **Alkylating agent**
      - **5-10 years – chromosome 5 and 7 abnormalities**
    - **Topoisomerase II inhibitors**
      - **1-2 years – 11q23 abnormalities**
    - **XRT (5-10 years)**
  - **Benzene exposure (organic solvents)**
  - **Smokers exposed to environmental agents (OR: 1.45)**

Prognostication

International Prognostic Scoring System (IPSS)

- **Multivariate analysis of hematologic characteristics of 816 patients at diagnosis**
  - **Also included patients with 20-30% blasts**
- **Identified 3 variables**
  - **% of bone marrow blasts**
    - **<5%; 5-10%; 11-20%, 21-29%**
  - **Cytogenetic abnormalities**
    - **Good: Normal, -Y, del(5q), del(20q)**
    - **Poor: Complex (≥3 abnormalities); abnormal Chr 7**
    - **Intermediate: All others**
  - **Number of cytopenias**
    - **ANC < 1800; Hemoglobin < 10; Platelets <100,000**

Greenberg P Blood 1997; 89: 29:2079

IPSS Scores and Associated Risk Groups

Risk Group	Score	Median Survival (years)	Median Time to AML evolution (years)
Low	0	5.7	9.4
Intermediate-1	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.2	1.1
High	≥2.5	0.4	0.2

Greenberg P Blood 1997; 89: 29:2079

Limitations of the IPSS

- Does not consider severity of cytopenias, just their presence
- Cytogenetic abnormalities were limited and not all patients are represented
- Not designed to use at later time points after diagnosis
- Excluded patients with secondary MDS, therapy-related MDS, and CMML
- Variability in outcomes of patients with lower risk disease

Revised International Prognostic Scoring System (IPSS-R)

- Cytogenetics (added 2 additional groups)
  - Very good: -Y or del(11q)
  - Good: CN, del(5q), del(12p), del(20q) or double abnormality including del(5q)
  - Intermediate: del(7q), +8,+19, i(17q) and any other single or double independent clones
  - Poor: -7, inv(3)/t(3q)/del(3q), double abnormalities including =7/del(7q) or 3 abnormalities
  - Very Poor: complex (≥3 abnormalities)
- Blast %
  - <2%, 2-5%, 5-10%, >10%
- Cytopenias
  - ANC, hemoglobin, and platelet count all now contribute to the score based on their severity

Greenberg PL Blood 2012; 120: 2454

Revised International Prognostic Scoring System (IPSS-R)

	Very Low	Low	Intermediate	High	Very high
Median Survival (years)	8.8	5.3	3.0	1.6	0.8
Median time to 25% AML transformation (years)	NR	10.8	3.2	1.4	0.73

Greenberg PL Blood 2012; 120: 2454

Case 2 continued

- IPSS score
  - Intermediate-2 risk group
  - Median survival of 1.2 years
- R-IPSS score
  - Very high risk group
  - Median survival of 0.8 years

Summary of Work-Up

- When to suspect?
  - Unexplained cytopenia
  - Symptoms may include fatigue, SOB, and bleeding or bruising depending on the cell lines involved
- Initial steps in diagnosis?
  - Comprehensive lab studies
  - Consider abdominal imaging if hepatosplenomegaly suspected
- When to refer to hematology?
  - New cytopenia and/or work-up has not shown source of cytopenia
  - If bone marrow biopsy felt to be indicated

Myelodysplastic Syndromes

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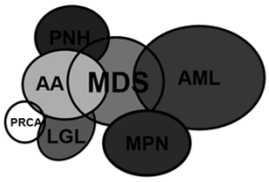
Pathogenesis and Treatment

MDS Overlaps with Other Entities



- MDS clinical and histopathological characteristics can overlap with many other hematological disorders
- An accurate diagnosis relies on expertise in interpreting diagnostic tests

Myelodysplastic Syndromes

- **Heterogenous group of malignant hematopoietic stem cell disorders**
- **Characterized by clonal hematopoiesis**
- **Quantitatively and qualitatively abnormal myeloid differentiation**
  - **Chronic cytopenias**
- **Immune dysregulation**
- **Variable progression to AML**

2016 WHO MDS Subtypes
MDS with single lineage dysplasia
MDS with multilineage dysplasia
MDS with Ringed Sideroblasts
MDS with RS with single lineage dysplasia
MDS-RS with multilineage dysplasia
MDS with isolated del(5q)
MDS with excess blasts
MDS-EB-1
MDS-EB-2
MDS, unclassifiable
With 1% blood blasts
With single lineage dysplasia and pancytopenia
Based on defining cytogenetic abnormality
Refractory cytopenias of childhood

Arber DA Blood 2016; 127:2391-2405

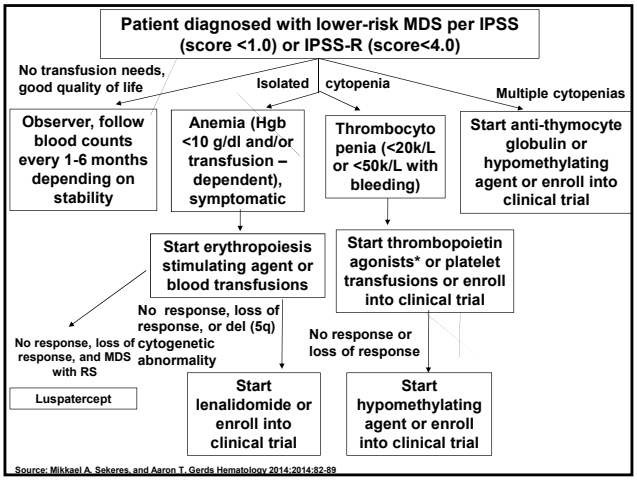
Chromosomal Abnormalities that diagnose MDS in Absence of definitive morphological criteria

Abnormality	Frequency, %
−5 or del(5q)	10-15
−7 or del(7q)	10
i(17q) or t(17p)	2-3
del(12p) or t(12p)	1-2
del(11q)	1-2
−13 or del(13q)	1-2
del(9q)	1
idic(X)(q13)	1
inv(3)(q21q26.2)	1
t(6;9)(p23;q34)	1
t(3;21)(q26.2;q22.1)	<1
t(1;3)(p36.3;q21.2)	<1
t(11;16)(q23;p13.3)	<1
t(2;11)(p21;q23)	<1

Pathogenesis

- **Unclear (? becoming clearer)**
  - **Involves the stepwise acquisition of oncogenic driver mutations**
    - **Thought to derive from a single transformed hematopoietic progenitor cell**
    - **>90% cases are associated with ≥ 1 driver mutation**
  - **Immune dysregulation**
  - **Abnormal marrow microenvironment**
  - **Alterations in DNA methylation/histone function**

Treatment



Anemia and Survival

- 1000 newly diagnosed patients with low and INT-1 risk MDS enrolled in European LeukemiaNet MDS registry (EUMDS)
  - 14 countries
  - Median age = 74 years
  - Most patients died without disease progression (higher risk/AML)
    - Infectious and cardiovascular
  - The mortality rate in transfusion dependent patients was 24% vs 5% in transfusion independent patients
    - Transfusion dependent patients with disease progression had a higher mortality rate than those who were not transfusion dependent at disease progression (66% vs 32%)
  - Transfusion dependent patients without disease progression and a serum ferritin $\geq$ 1000 µg/L had a higher mortality rate 56% vs 21% (HR 4.79, 95% CI 2.56-8.96) than transfusion independent patients
  - The degree of anemia appears to have an impact on OS and leukemia free survival

De Swart ASH Annual Meeting 2012; 120: 3830.

Erythropoietin Stimulating Agents

- Erythropoietin induces globin gene expression and promotes late erythroid differentiation
- Who responds?
  - Patients with lower risk MDS without ring sideroblasts had a higher probability of response
  - Higher response rates in patients without a prior transfusion need
  - Higher response in those with pre-treatment serum epo levels < 150-200

Serum Epo	Points	PRBCs/month	Points	Total Score	Likelihood of response
< 100	+2	< 2 Units	+2	> +1	74%
100-500	+1	> 2 Units	-2	-1 to +1	23%
> 500	-3			< -1	7%

Predictive model for response to erythropoietin and GCSF
Based on serum epo level and RBC transfusion requirement

Hellstrom-Lindberg E et al Br J Haem 2003; 120:1037-1046

Erythropoietin Stimulating Agents

- Response can take 8 weeks or more
- Duration of response and time to transfusion dependency is longer in patients treated within 6 months of diagnosis vs after 6 months
- Erythroid response to darbepoietin 56% at 24 weeks in lower risk MDS patients

Iron Overload

- Begins prior to patients becoming red cell transfusion dependent
  - Ineffective erythropoiesis suppresses hepcidin production in the liver → unrestrained intestinal iron uptake due to lack of inhibition of ferroportin (iron channel on basolateral surface of enterocytes)
- Iron toxicity may not only depend on the degree of iron accumulation but also on the extent of exposure to non-transferrin bound iron → increased oxidative stress

Malcovati L et al Haematologica 2006; 91: 1588-90

Iron Chelation

- Above a serum ferritin of 1000 ng/mL there is a dose dependent impact on OS 30% greater risk of death for every 500ng/mL increase in ferritin above 1000 ng/mL
- Recommendations for chelation are mostly based on expert opinion
  - Patients with a transfusion history of at least 20 or 25 units of PRBCs and serum ferritin > 1000
  - Focus on patients with lower-risk MDS who may have a longer life expectancy and will therefore receive long-term transfusion therapy
  - MRI is able to diagnose iron overload

Higher Risk Patients

- Early initiation of hypomethylating agent
  - Azacitidine or decitabine
  - CR rate of approximately 20%
  - 21 months versus 13 months of AML transformation when compared to Best Supportive Care
- Screen for HLA matched donor at diagnosis
  - Nonmyeloablative conditioning given age
  - Eligibility depends on preserved organ function, performance status, etc

Role of Allogeneic transplantation

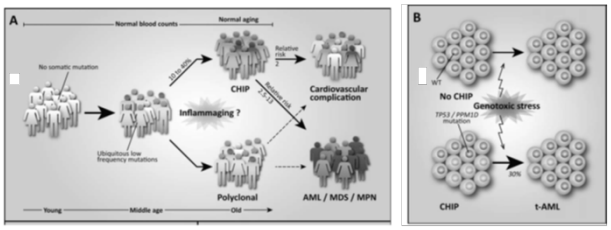
- 3rd most common indication for allogeneic stem cell/bone marrow transplantation
- Cutler et al. developed decision model to understand how treatment decisions affect overall outcome in patients with newly diagnosed MDS
  - Low/Int-1 IPSS patients – delay until progression
  - Int-2/High risk IPSS patients – early transplantation

Cutler et al. Blood. 2004 104: 579-585

Special Case

- A 52 year old female was found to have a new diagnosis of Stage III breast cancer and due to history of high risk family cancer, she sought genetic counseling.
- She underwent testing which included next generation sequencing of the blood.
- Results showed a *DNMT3A* mutation and her peripheral blood counts were normal at time of testing
- This result was consistent with Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Clonal Hematopoeisis of Indeterminate Potential



Condition characterized by the presence of a somatic mutation associated with a hematologic malignancy in the absence of definitive diagnostic criteria for neoplasm

Busque, L., Buscarlet, M., Mollica, L. and Levine, R.L. (2018), Concise Review: Age-Related Clonal Hematopoiesis: Stem Cells Tempting the Devil. Stem Cells, 36: 1287-1294. doi:10.1002/stem.2845

Idiopathic cytopenias of undetermined significance (ICUS)

- Describes patients in whom MDS is possible but not proven
- Must have relevant cytopenia in one or more lineage *hemoglobin <11 g/dL, neutrophil count <1500, platelet count <100,000 that persists for 6 months, cannot be explained by other disease and does not meet diagnostic criteria of MDS
- Patients should be carefully monitored

Slide 43

HP2 Janis - CHIP is more of a condition than a test, so I think this belongs in On Target (do we need to label all slides?)
Harty, Patrick, 5/21/2020

Special case continued

- She underwent treatment for her breast cancer with systemic chemotherapy and surgery.
- Approximately 5 years later, she began developing pancytopenia with WBC of 1.5, Hgb 10.0, and platelet count of 89,000. Her MCV was 105.
- She underwent a bone marrow biopsy for work-up and was consistent with MDS-EB-1 with 9% blasts.
- Cytogenetics were complex with NGS showing a new *TP53* mutation along with her known *DNMT3A* mutation.
- Diagnosis was consistent with therapy-related MDS and patient was initiated on azacitidine

Special case continued

- The patient underwent bone marrow re-assessment after 2 cycles of therapy and was found to have progression to AML with 24% blasts.
- Bone marrow biopsy showed no change in cytogenetics or NGS results from prior testing.
- She is now undergoing treatment with liposomal daunorubicin and cytarabine for AML with MDS-related changes.

Conclusions

- MDS is a heterogeneous disease
  - Mutational analysis will likely improve our ability to risk stratify patients better and potentially give more targeted therapeutics
- Consideration of ESA therapy in patients with low risk disease with anemia only is reasonable
- Consider lenalidomide in patients with 5q abnormalities
- Consider luspatercept in MDS with Ringed Sideroblasts who are transfusion-dependent and not/lost response to ESA therapy
- 5-azacytidine is the only available hypomethylating agent with a proven survival advantage
- Consider BMT referral in patients with higher risk disease