Could this patient have myelodysplastic syndrome?

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Disclosures

FINANCIAL DISCLOSURE

Grants/Research Support: Nil

Speaker bureau/Honoraria: Novartis

Advisory boards: Celgene, Roche

Consulting fees: Nil
Objectives

1. Know when to suspect myelodysplastic syndrome (MDS) in patients presenting with cytopenias.
2. Be familiar with the diagnostic approach and criteria to establish a diagnosis of MDS
3. Be aware of the treatment options and prognosis for patients with MDS
Myelodysplastic Syndromes (MDS)

- **MDS**: group of clonal myeloid neoplasms characterized by one or more peripheral blood **cytopenias** + morphologic **dysplasia** in hematopoietic cells (in bone marrow)

- **Causes of cytopenias:**
  - Many etiologies: as shown in algorithms for various cytopenias.

- **Reactive causes of dysplasia:**
  - Many: nutritional deficiencies, cytotoxic therapy, infections, inflammation

- Even normal individuals may have dysplasia
Dysplasia in bone marrow cells

- **Reactive causes of dysplasia:**
  - Vit def: B12, folate, pyridoxine
  - Drugs: chemo, methotrexate, azathioprine
  - Infections: sepsis, viral, TB
  - Alcohol, Inflammation

- Identification of dysplasia not always reproducible: **inter-observer variation**
Diagnosis MDS (WHO criteria)

<table>
<thead>
<tr>
<th><strong>Peripheral blood</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytopenias (one or more): Hb &lt;100 g/L; Plat &lt;100 x10^9/L; ANC &lt;1.8 x10^9/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>+ Bone Marrow</strong></th>
</tr>
</thead>
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<tr>
<td>Dysplasia: 10% or more in erythroid, myeloid or megakaryocytes OR</td>
</tr>
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<td>Myeloblasts: ≥ 5% (or ≥ 1% in blood) OR</td>
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<td>Cytogenetics: MDS defining, by conventional karyotyping</td>
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Exclude Reactive Causes of Dysplasia

Who should be referred for investigation of MDS?
Criteria for Observation vs Urgent or Emergent referral given in Algorithms for Anemia, Leucopenia, Thrombocytopenia and Pancytopenia

MDS is one of the causes of cytopenias

Diagnosis of MDS should be made in a Hematology Centre

MDS more likely in:
• Elderly (median age 70)
• Unexplained macrocytic anemia
• Previous myelotoxic drugs, radiation

Classification and Management of MDS is Evolving
### Myelodysplastic syndrome (MDS)
- Refractory cytopenia with unilineage dysplasia
  - Refractory anemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome

*Provisional entity: refractory cytopenia of childhood*

### 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*
Referral to Hematology

• 52M, had travelled North, developed shortness of breath → Hb 45g/L. Transfused blood and referred for Inv Anemia.
• No history of blood loss or jaundice. Clinical: pallor, no other finding
• Hb 66g/L WBC 6.3 x10⁹/L, Neutr 6.2 x10⁹/L Plate 255 x10⁹/L, retic 0.50%, retics:12.6 x10⁹/L, MCV 95.2fl, MCH 30.7pg.
• Ferritin 1128, LDH 186
• Bone marrow: Refractory cytopenia with multilineage dysplasia (RCMD)
• BM cytogenetics: 46 XY, del (5q)
• Diagnosis: MDS – del (5q)
• ? Prognosis ? Treatment
Risk Stratification by Prognostic Scoring

1997 International Prognostic Scoring System (IPSS)

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Karyotype class*</td>
<td>0.5</td>
</tr>
<tr>
<td># of cytopenias**</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
</tr>
</tbody>
</table>

- *Karyotype risk groups: Good = normal, −Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes
- **Qualifying Cytopenias: Hb < 10 g/dL, ANC < 1800/µL, platelets < 100,000/µL
- ***20% or more blasts now (WHO) considered AML, but was still MDS (FAB) at the time this system was developed

Score sum | IPSS Risk Category | Median survival for over age 60 group (years) | Time until 25% get AML (years)
---------------------------------|------------------|---------------------------------------------|--------------------------
0 | Low | 5.7 | 9.4 |
0.5-1.0 | Int-1 | 3.5 | 3.3 |
1.5-2.0 | Int-2 | 1.2 | 1.1 |
>2.5 | High | 0.4 | 0.2 |


IPSS-R

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Categories and Associated Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic risk group</td>
<td>Very good</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10 g/dL</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>≥0.8 x 10⁹/L</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥100 x 10⁹/L</td>
</tr>
</tbody>
</table>

Possible range of summed scores: 0-10


IPSS-R

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>% patients (n=7,012; AML data on 6,485)</th>
<th>Median survival, years</th>
<th>Median survival for pts under 60 years</th>
<th>Time until 25% of patients develop AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>2.0-3.0</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3.5-4.5</td>
<td>20%</td>
<td>3.0</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>5.0-6.0</td>
<td>13%</td>
<td>1.5</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6.0</td>
<td>10%</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Using IPSS-R: 27% of IPSS lower risk “upstaged” 18% of IPSS higher risk “downstaged”

Risk Stratification in MDS

According to Scoring Systems
IPSS/IPSS-R/WPSS/MPSS

Lower risk
- Mild cytopenias
- Low blast counts
- “good” cytogenetics

Higher risk
- Severe cytopenias
- High blast counts
- “poor” cytogenetics

Our Patient had IPSS score: 0, Low Risk
Supportive Care: at all stages and if specific treatment fails
RBC transfusion, Fe chelation
Platelet transfusion (for thrombocytopenia); Antibiotics for neutropenic infections
Our Patient: MDS del (5q)

- Sr erythropoietin 600 IU/ml.
- Lenalidomide not available in early 2009.

Rx
- Regular packed cell transfusions: 4-6 per month.
- Increase in iron and ferritin
- Added iron chelator: Deferasirox
Course of Illness

- 2010: Lenalidomide available.
- Sustained rise in Hemoglobin
- Hb range: 140-160g/L
- After 6 months, repeat bone marrow: Complete Remission (CR). Normal cytogenetics
- Deferasirox stopped
- Phlebotomy 500ml once a month → ferritin normal
Four years later….

- Gradual decrease in Hb, WBC, ANC and platelets.
- Transfusion dependent
- Lenalidomide stopped
- Bone marrow: MDS, blasts 12%, cytogenetics del (5q)
- Diagnosis: **Refractory Anemia with Excess Blasts-2 (RAEB-2)**
- ?Prognosis
- ?Treatment
Therapeutic Algorithm

Lower risk MDS

Age ≥ 65-70 y
Or poor performance status
Not eligible for transplant

Higher Risk MDS

Age ≤ 65-70 y
Good performance status

Stem cell donor available

≥ 10% BM Blasts
Azacitidine or AML-like chemo

<10% BM Blasts
Allogeneic Stem Cell Transplant (BMT) (only curative treatment)

No Stem cell donor

≥ 10% BM Blasts
Azacitidine

<10% BM Blasts
Supportive Care as needed
Our Patient: managing progression to high-grade MDS

Rx
- Azacitidine (hypomethylating agent)- Outpatient Rx
  - Inj 75mg/m² S/C once a day x 7 days (every 28 days)
- After 3 cycles: repeat BM → no response

Azacitidine increases overall survival. Response is slow; Improvement in 50% cases.

- Admit to HSC – GD6 ward: Intensive chemotherapy (as for AML)
  - Daunorubicin + Cytarabine
- After 4 weeks: No response, BM Blasts 9.8%.
Further therapy: Allogeneic stem cell transplant

- Matched unrelated donor (MUD) identified
- Risks of transplant explained:
  - Toxicity of procedure
  - Graft versus host disease (GVHD)
  - Relapse of MDS
- Admitted to GD6 for transplant
  - Myeloablative conditioning (to eliminate disease and clones)
  - Infused donor peripheral blood stem cells
  - Hematopoietic recovery in 14 days
- Discharged home: developed GVHD
- Repeat Bone marrow: Normal (100% Donor)
- Outcome:
  - Cured of MDS
  - Suffering from GVHD

Most of the monitoring and support by the CCP Physician and Family doctor
Take Home Messages

• MDS presents with gradual onset of anemia, or other cytopenias, usually in elderly
• Diagnosis should be made in a hematology center, BM exam is critical.
• Therapy is evolving, but majority will be managed primarily with supportive therapy
• The Family physician has a crucial role in managing along with the hematologist
Algorithm for Myelodysplastic Syndrome (MDS)

MDS is one of the causes of cytopenias
Criteria for Observation vs Urgent or Emergent referral given in Algorithms for Anemia, Leucopenia, Thrombocytopenia and Pancytopenia

DIAGNOSIS: Peripheral Blood: (1) Cytopenia(s): Hb<100g/L; Platelets <100x10^9 /L; ANC <1.8 x10^9/L
AND (2) Bone Marrow (BM): Dysplasia: 10% or more in erythroid, myeloid or megakaryocytes OR Myeloblasts ≥5% (or ≥1% in blood) OR Cytogenetics MDS defining (by conventional karyotyping)
(3) Exclude Reactive Causes of dysplasia

MDS more likely in: Elderly (median age 70 years), Unexplained macrocytic anemia, Previous myelotoxic drugs, radiation.
Even normal individuals may have dysplasia. Identification of dysplasia not always reproducible (i.e. inter-observer variation). Diagnosis of MDS should be made in a Hematology Centre.

Risk Stratification according to Scoring Systems (IPSS / IPSS-R / WPSS / MPSS)

Lower Risk
(Mild cytopenias; Low blast counts; "Good" cytogenetics)

Asymptomatic

Symptomatic Anemia

Watch and Monitor
Every 3 months

MDS del (5q)

S EPO<sub>r</sub> < 500mU/ml
± RBC Transfusion < 2/month

MDS del (5q)

S EPO<sub>r</sub> ≥ 500mU/ml
± RBC Transfusion ≥ 2/month

MDS del (5q)

Trial of ESA<sup>+</sup>
± G-CSF

Trial of ESA<sup>+</sup>
± G-CSF

Lenalidomide

Trial of ESA<sup>+</sup>
± G-CSF

Immunosuppressive therapy

Supportive Care at all stages: RBC transfusion, Platelet transfusion (for thrombocytopenia); Antibiotics for neutropenic infections; Fe chelation

Higher Risk
(Severe cytopenias; High blast counts; "Poor" cytogenetics)

Age ≤ 65-70y
Good performance status

Age > 65-70y
Or poor performance status

Not eligible for transplant

Donor available?

YES

BM blasts

≥ 10% BM blasts

Allogeneic Stem Cell Transplant (BMT)
(only curative treatment)

Azacitidine OR
AML-like chemotherapy

NO

< 10% BM blasts

Azacitidine

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.
References


MDS Clear Path:
A Canadian physician Consensus
http://www.mdsclearpath.org/

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Myelodysplastic Syndromes
NCCN.org
Questions?

rkumar@cancercare.mb.ca
A 64 year man was detected to have hemoglobin 60g/L (requiring 4 units packed cells per month), retics 0.5%, normal leucocytes, platelets, B12, folate and chemistry. Bone marrow shows significant dysplasia, no increase in blasts, chromosome analysis showed deletion 5(q).

What is the best treatment?

a) Hematopoietic stem cell transplant (Bone marrow transplant)
b) Erythropoietin 40,000Units subcutaneous / week.
c) Lenalidomide
d) Azacitidine
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