Case 2

65 yr old male had gradual onset of “odd” behavior with psychotic symptoms, irritability and parasthesia in hands and feet. He was noticed to have imbalanced gait. Examination showed loss of vibration and proprioception in lower limbs.
Laboratory tests

Hb 5 g/dl, MCV 112,

Retics (corrected) 0.009

WBC 3.3k, Platelets 112k

LDH 1900. Serum B12 30pg/ml.

IF Ab +PCA+

Achlorhydria+

Gastric Bx atrophic gastritis.
Physical And Lab

Red Beefy Tongue

Vitiligo

Macro-ovalocytes

BM: Megaloblasts

Oxyntic G. mucosa atrophy
1-PA is the end-stage of Atrophic Body Gastritis (ABG) causing oxyntic gastric mucosa damage: achlorhydria.

2-It is considered an autoimmune disease (AID).

3-AID theory is based on the presence of parietal cell and/or intrinsic factor autoantibodies. Frequent association with other autoimmune disorders: autoimmune thyroid disease (ATD), type 1 diabetes, and vitiligo.
Diagnosis of pernicious anemia

- Atrophic body gastritis
  - Serological markers:
    - Increased fasting gastrin
    - Reduced levels of pepsinogen
  - Histological confirmation by bioptic sampling of gastric body mucosa

- Intrinsic factor deficiency

- Cobalamin deficiency + macrocytic anemia
  - Blood tests:
    - Complete blood count
    - Serum cobalamin levels
  - Schilling test (obsolete) or serological markers for pernicious anemia:
    - Intrinsic factor antibodies
    - Parietal cell antibodies
A-Before therapy

B-Post-therapy

A- Hyperintense in cervical region

B-corrected
Subacute Combined Degeneration of Spinal Cord

Degeneration of posterior & lateral column
Other causes of cobalamin deficiency

Gastric causes of impaired absorption:
Gastrectomy/ gastric sleeve operations

Corpus-predominant *H pylori* gastritis

Long-term proton pump inhibitor therapy

Ileal disease or resection

Blind loop syndrome
Fish tapeworm
Severe pancreatic insufficiency
Decreased intake due to vegetarianism
Other causes of macrocytic anemia

Folate deficiency

Drugs (e.g. methotrexate, azathioprine, 6-mercaptopurine)

erythropoiesis: hemolysis, response to hemorrhage

Liver disease (alcoholic, cirrhosis, poor dietary intake)

Hypoplastic anemia, myelodysplastic syndrome

Chronic obstructive pulmonary disease
Case 2 : Treatment & Monitoring

No Blood Transfusion
Vit B12 IM injections daily 7-10 days. Then monthly lifelong.

Careful monitoring of response
Careful monitoring for gastric Ca
Careful monitoring for thyroid function & DM
Response to Treatment

Reticulocytosis in 3-4 days, peak 5-10 days
Rise in Hgb concentration within 10 days and normalization in 8-10 weeks as well as correction of MCV.
Fall of serum LDH levels within 2 days
Hypersegmented PMN disappear in 10-14 days
Watch closely for severe hypokalemia during early response.
Megaloblastic changes disappear within 2 days
Case 2 B

65 yr old male had “anemia syndrome” over the last 6 weeks. He noticed abdominal swelling and weight loss. He had mild fever and night sweats for 2 weeks. No neurological symptoms or signs.

Hb 9, MCV 106, WBC 5.3, Plt 142, Retics (corrected)0.1%. Serum B12 normal. LDH 1100. Serum folate was 0.2

Abdominal Ct

Biopsy (undif. sarcoma)
Causes of Folic acid deficiency

1. Inadequate intake
   - diet lacking fresh, uncooked food; chronic alcoholism, total parenteral nutrition,

2. Malabsorption
   - small bowel disease (sprue, celiac disease)
   - alcoholism

3. Increased requirements:
   - pregnancy and lactation
   - infancy
   - chronic hemolysis
   - malignancy
   - hemodialysis

4. Defective utilisation
   Drugs: folate antagonists (methotrexate, trimethoprim, triamteren), purine analogs (azathioprine), primidine analogs (zidovudine), RNA reductase inhibitor (hydroxyurea), miscellaneous (phenytoin, N₂)
Case 2 B:  
Treatment and follow-up

Treat the original Cause  
Oral administration of folic 5 mg x2daily, for 3 months, and maintenance therapy if it is necessary.  
Retics after 5-7 days.  
Correction of anaemia after 2 months therapy.
Folic acid has role in neural tube closure in foetus, a pregnant woman should have enough folate to protect her foetus from having neural tube defects.
Case 2 C

48 yr old lady presented with “anemia syndrome” for 3 months. She was found to have splenomegaly. Hb 8g, MCV 107fl, WBC 3.6, plt 95k, retics 0.6%. LDH 350
BM: ringed sideroblasts, blasts 8%. Cytogenetics by FISH 11 q del.

Diagnosis: MDS: RARS/RAEB type I with ring sideroblasts
What are MDS?

- MDS: a spectrum of heterogeneous malignant hematopoietic stem cell disorders characterized by ineffective and dysplastic changes in BM with
  - ineffective haemopoiesis - dysmorphic cells in blood
  - Variable cytopenia - frequent progression to AML
- MDS may occur
  a-de novo: primary MDS b-as a result of haemopoietic stem cell injury: secondary or treatment-related MDS
- MDS is associated with significant morbidity and mortality due to
  - cytopenias
  - impaired quality of life
  - risk of transformation to AML
Epidemiology of MDS

• Epidemiology of MDS
  – common bone marrow disorder
  – the overall incidence is approximately 5 per 100,000 in the general population
  – peak incidence occurs at 60–90 years of age
    > 20 per 100,000 at 70 years of age

• Typical MDS patient
  – elderly
  – slight male preponderance
  – approximately 50% have a cytogenetic abnormality
Age-related Incidence of MDS
Leukaemia Research Fund [1984-1993]

Reprinted with Permission of Leukemia Research Fund
Pathogenesis

Poorly understood
Clonal process, thought to arise from single hematopoietic progenitor cell that acquired multiple mutations
Global hypomethylation with concomitant hypermethylation of gene-promoter regions.
Mutation in genes that encode enzymes, such as TET2, IDH1, IDH2
As role for immunosuppressive agents, suggest immune system implicated in myelosuppression and/or marrow hypocellularity
Clinical features in MDS

• Anaemia
  – > 80% of patients with MDS are anaemic at diagnosis
  – Granulocytopenia
  – 50–70% of patients
  – predisposition for infections
• Thrombocytopenia in 30% of patients
• In MDS
  – chronically low Hb levels associated with cardiac remodelling and increased incidence of heart failure
Diagnosing MDS

Cytopenia(s) → suspect MDS

Recommended evaluations

- History and physical examination
- Complete blood, platelets, differential, and reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics
- Serum erythropoietin (prior to RBC transfusion)
- RBC folate and serum vitamin B_{12}
- Serum ferritin
- Documentation of transfusion history

Diagnosis of MDS based on morphologic and clinical criteria
## Subtypes of MDS: WHO classification

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anaemia (RA)</td>
<td>Anaemia, No or rare blasts, $&lt; 1 \times 10^9$/L monocytes</td>
<td>Erythroid dysplasia only,  $&lt; 10%$ grans or mega dysplastic, $&lt;5%$ blasts, $&lt;15%$ ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anaemia with ringed sideroblasts (RARS)</td>
<td>Anaemia, No blasts</td>
<td>Erythroid dysplasia only,  $&lt;10%$ grans or mega dysplastic, $\geq 15%$ ringed sideroblasts, $&lt;5%$ blasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenias (bicytopenia or pancytopenia), No or rare blasts, No Auer rods, $&lt; 1 \times 10^9$/L monocytes</td>
<td>Dysplasia in $\geq 10%$ of cells in two or more myeloid cell lines, $&lt;5%$ blasts in marrow, no Auer rods, $&lt;15%$ ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)</td>
<td>Cytopenias (bicytopenia or pancytopenia), No or rare blasts, No Auer rods, $&lt; 1 \times 10^9$/L monocytes</td>
<td>Dysplasia in $\geq 10%$ of cells in two or more myeloid cell lines, $\geq 15%$ ringed sideroblasts, $&lt;5%$ blasts, no Auer rods</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopenias, $&lt; 5%$ blasts, No Auer rods, $&lt; 1 \times 10^9$/L monocytes</td>
<td>Unilineage or multilineage dysplasia, $5–9%$ blasts, no Auer rods</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenias, $5–19%$ blasts, Auer rods $\pm$, $&lt; 1 \times 10^9$/L monocytes</td>
<td>Unilineage or multilineage dysplasia, $10–19%$ blasts, Auer rods $\pm$</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Cytopenias, No or rare blasts, no Auer rods</td>
<td>Unilineage gran or mega dysplasia, $&lt;5%$ blasts, no Auer rods</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Anaemia, $&lt; 5%$ blasts, Platelets normal or increased</td>
<td>Normal to increased megakaryocytes with hypolobulated nuclei, $&lt;5%$ blasts, no Auer rods, isolated del(5q)</td>
</tr>
</tbody>
</table>
Frequencies of the most common cytogenetic anomalies in patients with MDS

Point Mutations in MDS

Tyrosine Kinase Pathway
- JAK2
- KRAS
- BRAF
- NRAS
- RTK’s
- PTPN11
- CBL

Transcription Factors
- RUNX1
- ETV6
- WT1
- PHF6
- GATA2
- EP300
- IDH 1 & 2

Others
- TP53
- NPM1
- Cohesins
- GNAS/GNB1
- RNA helicases
- BCOR
- SRSF2
- U2AF1
- ZRSF2
- PRPF40B
- U2AF2
- PRPF8
- SF3A1

Epigenetic Dysregulation
- DNMT3A
- EZH2
- UTX
- SETBP1
- IDH 1 & 2
- TET2
- ASXL1
- ATRX

Splicing Factors
- SRSF2
- SF3B1
- SF1
- SF3A1
- U2AF1
- U2AF2
- PRPF8
- PRPF40B
Many mutations are very rare

Only 5 genes are mutated in >10% of patients
### WHO classification-based Prognostic Scoring System (WPSS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO category</td>
<td>RA, RARS, isolation 5q−</td>
<td>RCMD, RCMD-RS</td>
<td>RAEB-1</td>
<td>RAEB-2</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>–</td>
</tr>
<tr>
<td>Transfusion</td>
<td>No</td>
<td>Regular</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>requirement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Karyotype: **good**: normal, -Y, del(5q), del(20q); **poor**: complex (≥ 3 abnormalities), chr 7 anomalies; and intermediate: other abnormalities.

<table>
<thead>
<tr>
<th>Score</th>
<th>WPSS subgroup</th>
<th>Median survival (months) Italian cohort</th>
<th>Median survival (months) German cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Very low</td>
<td>103</td>
<td>141</td>
</tr>
<tr>
<td>1</td>
<td>Low</td>
<td>72</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>3–4</td>
<td>High</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>5–6</td>
<td>Very high</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

Case 2 C

WPSS
WHO category = 2
Cytogenetics intermed. = 1
Bld Trx = 0
Total score 3. ms 21-26 months
MDS: therapeutic options

- "Best supportive care", including iron chelation
- Haemopoietic growth factors
- Immunosuppressive treatment
- Differentiation induction
- Immunomodulatory drugs
- Arsenic trioxide
- Low-dose chemotherapy
- Epigenetic treatment
- Intensive chemotherapy
- Allogeneic SCT

SCT = stem cell transplantation.
proposed general treatment algorithm

Treatments can be complicated by advanced age, comorbidities, chronicity of the disease.

Treatment Algorithm for Patients With MDS

**Low/Int-1**
- **Asymptomatic**
- Observation
- Cytokine Epo/G-CSF
- Azacitidine
- Thalidomide

**Int-2/High**
- **Symptomatic**
- BM Function
- Transfusion
- SCT—ablative
- RIC
- Investigational
- Azacitidine
- Thalidomide
- 5q-
- 8+
- 5/7-, 7q Complex
- Intensive chemotherapy
- SCT—full ablative-RIC
- RIC = reduced intensity conditioning.