

# What's in a name?

Classification of myelodysplastic  
and myeloproliferative disorders

# What is myelodysplastic syndrome (MDS)?

- An acquired disorder of blood cell production that may develop into acute leukemia
- Can occur de novo or after chemotherapy or radiation therapy
- Characteristic morphologic changes in the peripheral blood and bone marrow
- Usually has a cytogenetic abnormality
- Patients present with too few red blood cells, neutrophils, or platelets

# Myelodysplastic Syndrome (MDS) and cancer registries

- Minimal epidemiologic data on MDS because of little reporting to cancer registries and difficulties in recognizing the diagnosis
- No classification system until 1982 (FAB)
- New classification system in 2001 (WHO)
- *Pathologists and oncologists may not always use a WHO diagnosis in their report*

# History of MDS

- Recognized since early 1900's that some patients have prolonged cytopenias (e.g. too few red blood cells, white blood cells and or platelets) before developing leukemia – termed “refractory anemia”
- A number of terms were used to describe this phenomenon, including “preleukemia”, introduced in the 1950's

# Myelodysplastic Syndrome

- In 1976, the French-American-British classification of acute leukemias recognized a disorder of dysfunctional hematopoiesis often leading to acute leukemia termed “myelodysplastic syndrome” (MDS)
- In 1982, they proposed a classification system for MDS

# How does a pathologist diagnose myelodysplastic syndrome?

- Clinical history of prolonged, unexplained anemia, neutropenia or thrombocytopenia
- Abnormal looking (dyspoietic or dysmorphic) cells in the bone marrow or peripheral blood
- Morphologic evidence of ineffective hematopoiesis (hypercellular marrow, disordered, abnormal iron accumulation in red blood cell precursors- ringed sideroblasts)
- +/- an increase in blasts, but not enough for a diagnosis of acute myeloid leukemia
- Clonal cytogenetic abnormality

# Myelodysplastic Syndrome

## FAB classification of MDS, 1982

### – Refractory anemia

- Cytopenia (anemia, neutropenia or thrombocytopenia) with with  $\leq 1\%$  blasts in blood,  $< 5\%$  blasts in BM, and  $< 15\%$  ringed sideroblasts
- Monocytes  $< 1 \times 10^9/L$

- Refractory anemia with ringed sideroblasts
- Refractory anemia with excess of blasts
- Refractory anemia with excess of blasts in transformation
- Chronic myelomonocytic leukemia

# Myelodysplastic Syndrome

## FAB classification of MDS, 1982

- Refractory anemia
- **Refractory anemia with ringed sideroblasts**
  - Cytopenia with  $\leq 1\%$  blasts in blood,  $< 5\%$  blasts in BM, and  $> 15\%$  ringed sideroblasts in the BM
  - Monocytes  $< 1 \times 10^9/L$
- Refractory anemia with excess of blasts
- Refractory anemia with excess of blasts in transformation
- Chronic myelomonocytic leukemia

# Myelodysplastic Syndrome

## FAB classification of MDS, 1982

- Refractory anemia
- Refractory anemia with ringed sideroblasts
- **Refractory anemia with excess of blasts**
  - Cytopenia with 1-5% blasts in the blood or 5-19% blasts in the bone marrow
  - Monocytes  $< 1 \times 10^9/L$
- Refractory anemia with excess of blasts in transformation
- Chronic myelomonocytic leukemia

# Myelodysplastic Syndrome

## FAB classification of MDS, 1982

- Refractory anemia
- Refractory anemia with ringed sideroblasts
- Refractory anemia with excess of blasts
- Refractory anemia with excess of blasts in transformation
  - Cytopenia with  $\geq 5\%$  blasts in the blood, 20-29% blasts in marrow, or blasts containing Auer rods in the blood or bone marrow
- Chronic myelomonocytic leukemia

# Myelodysplastic Syndrome

## FAB classification of MDS, 1982

- Refractory anemia
- Refractory anemia with ringed sideroblasts
- Refractory anemia with excess of blasts
- Refractory anemia with excess of blasts in transformation
- **Chronic myelomonocytic leukemia**
  - <5% blasts in the blood or <20% blasts in the bone marrow
  - Monocytes > 1 x 10<sup>9</sup>/L in the blood

# Why did they need a new classification?

- Each FAB subgroup was heterogeneous
  - Variable lineage involvement (erythroid, granulocytic or megakaryocytic)
  - Various cytogenetic abnormalities
  - Widely variable clinical outcomes

# Major changes to FAB by the WHO

1. Lowered the threshold for defining acute myeloid leukemia to 20% blasts in the bone marrow or blood, eliminating the RAEB-T
  - Divided low grade categories of refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS) into 5 separate entities, depending on:
    - single versus multilineage dysplasia
    - Presence or absence of an isolated interstitial deletion of chromosome 5q

# Major changes to FAB by the WHO

2. Divided low grade categories of refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS) into 5 separate entities, depending on:

- single versus multilineage dysplasia
- Presence or absence of an isolated interstitial deletion of chromosome 5q

# Major changes to FAB by the WHO

3. Subdivided refractory anemia with excess blasts (RAEB) into two categories depending on the percentage of blasts in the blood or marrow

- RAEB-1

- <5% blasts in the peripheral blood
- 5-9% blasts in the bone marrow

- RAEB-2

- 5-19% blasts in the peripheral blood
- 10-19% blasts in the bone marrow

# Major changes to FAB by the WHO

4. Removed chronic myelomonocytic leukemia from the MDS category, and placed it into a new category of myelodysplastic/myeloproliferative disorder overlap diseases.

# Myelodysplastic Syndrome

## FAB classification, 1982

- Refractory anemia
- Refractory anemia with ringed sideroblasts
- Refractory anemia with excess of blasts
- Refractory anemia with excess of blasts in transformation (now AML)
- Chronic myelomonocytic leukemia (moved to MDS/MPD overlap)

## • WHO Classification, 2002

- Refractory anemia
- Refractory cytopenia with multilineage dysplasia
- 5q(-) syndrome
- Myelodysplastic syndrome, not otherwise specified
- Refractory anemia with ringed sideroblasts
- Refractory anemia with excess of blasts
  - Type I
  - Type II

# WHO classification

	Peripheral Blood	Bone Marrow
Refractory Anemia (RA) 9980/3	Anemia No or rare blasts	Erythroid dysplasia only <5% blasts <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts 9982/3	Anemia No blasts	≥15% ringed sideroblasts Erythroid dysplasia only <5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD) 9985/3	Cytopenias (bi- or pancytopenia) No or rare blasts No Auer rods <1 x 10 <sup>9</sup> /L monocytes	Dysplasia in ≥10% of the cells of two or more myeloid cell lines <5% blasts No Auer rods
Myelodysplastic syndrome, unclassifiable 9989/3	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia, non-erythroid <5% blasts No Auer rods

# WHO classification

	Peripheral Blood	Bone Marrow
Refractory anemia with excess blasts-1 (RAEB-1) 9983/3	Cytopenias <5% blasts No Auer rods <1 x 10 <sup>9</sup> /L monocytes	Unilineage or multilineage dysplasia 5-9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2) 9983/3	Cytopenias 5-19% blasts Auer rods +/- <1 x 10 <sup>9</sup> /L monocytes	Unilineage or multilineage dysplasia 10-19% blasts Auer rods +/-
MDS associated with isolated del 5(q) 9986/3	Anemia Usually normal or increased platelet count <5% blasts	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

# Older synonyms

- *MDS*
  - Dysmyelopoietic syndrome
  - Preleukaemic syndrome
  - Oligoblastic leukemia
- *Refractory anemia*
  - Aregenerative anemia
- *Refractory anemia with ringed sideroblasts*
  - Pure sideroblastic anemia
  - Acquired idiopathic sideroblastic anemia
  - Sideroblastic anemia

# Isn't a biopsy the final answer?



# Isn't a biopsy the final answer?

## MOST TUMORS

A patient with a solid tumor usually presents with a mass. After a biopsy, the pathologist can (usually) tell if it is a reactive process like inflammation, a benign tumor or a malignant tumor.



BIOPSY=ANSWER

## MYELODYSPLASTIC SYNDROME

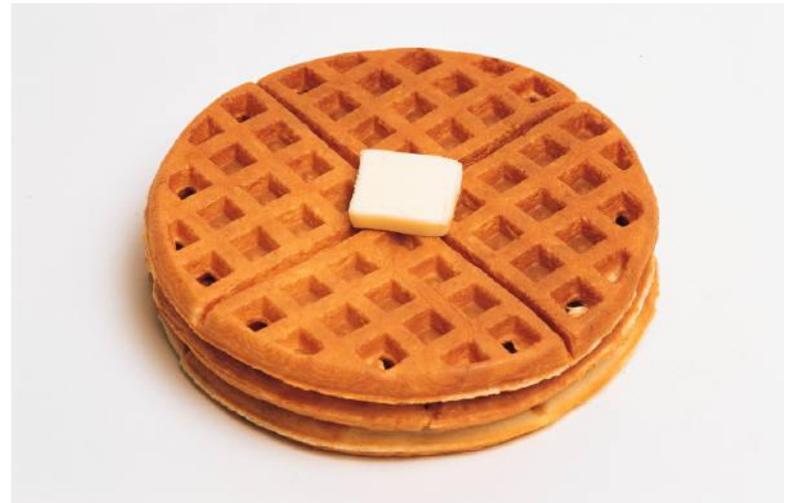
Patients with MDS present with anemia, neutropenia or thrombocytopenia. The bone marrow biopsy may show changes that suggest myelodysplastic syndrome, but they are not specific.

BIOPSY=SUGGESTION

For a diagnosis, you need cytogenetics and clinical correlation.

# Why do pathologists waffle and not just use a WHO diagnosis?

- A pathology report may be signed out as
  - Dyspoiesis
  - Dyserythropoesis
  - Dysgranulopoesis
  - Dysmegakaryopoesis
  - Dysplastic features
  - Megaloblastic features



***The morphologic changes are not specific, many non-neoplastic potential causes need to be clinically excluded.***

# Things that can mimic MDS

- Normal marrow -rare dyspoietic cells are in normal bone marrows (should see >10% of a lineage involved to call MDS)
- B12/folate deficiency
- Congenital dyserythropoietic anemia
- Toxins (arsenic, alcohol)
- Chemotherapy
- Growth factor therapy
- HIV infection
- Parvovirus B19 infection
- Increased hematopoiesis (stress hematopoeisis)
- Poor quality specimen

# Confusing similar sounding diagnoses

- *Sideroblastic anemia*
  - Not the same as refractory anemia with ringed sideroblasts. Sideroblastic anemia is a broad group of disorders including RARS, but only RARS is neoplastic and reportable.
  - Need a specific diagnosis of RARS

# Confusing similar sounding diagnoses

- *Myelodysplasia*

- A congenital defect of the spinal cord and nerves – NOT |



- A clinician could use this word generically for ineffective hematopoiesis when the cause may not necessarily be MDS.

# Myelodysplastic /Myeloproliferative diseases

Neoplasms with some features of MDS and some features of a chronic myeloproliferative disease at presentation.

- Chronic myelomonocytic leukemia 9945/3
- Atypical chronic myeloid leukemia 9876/3
- Juvenile myelomonocytic leukemia 9946/3
- Myelodysplastic/myeloproliferative, unclassifiable, 9975/3

# Chronic myelomonocytic leukemia

1. Persistent peripheral blood monocytosis  $>1 \times 10^9/L$
2. No Philadelphia chromosome or BCR/ABL fusion gene
3. Fewer than 20% blasts in the blood or bone marrow.
4. Dysplasia in one or more myeloid lineages. If dysplasia is minimal, need:
  - Clonal cytogenetic abnormality
  - Persistence of monocytosis  $>3$  months
  - All other causes of monocytosis have been excluded

# Chronic myelomonocytic leukemia

## Synonyms:

Subacute myelomonocytic leukemia

Chronic myelomonocytic syndrome

## Subtypes:

*CMML-1* : blasts <5% in the blood, <10% in the bone marrow

*CMML-2*: blasts 5-19% in the blood or 10-19% in the bone marrow, or Auer rods present with <20% blasts

*CMML with eosinophilia*

# Atypical chronic myeloid leukemia

1. Peripheral blood leukocytosis with increased mature and immature neutrophils
2. Prominent dysgranulopoiesis
3. No Ph chromosome or *BCR/ABL* fusion
4. Neutrophil precursors  $\geq 10\%$  of WBC
5. No basophilia, basophils  $< 2\%$  of WBC
6. No monocytosis, monocytes  $< 10\%$  of WBC
7. Hypercellular marrow with myeloid hyperplasia and dysplasia of myeloids, with or without dysplasia of erythroids or megakaryocytes
8. Fewer than 20% blasts in blood or bone marrow

# Atypical chronic myeloid leukemia

Relatively new entity

## Synonyms

Subacute myeloid leukemia

## Variants

“Syndrome of abnormal chromatin clumping”

# Juvenile myelomonocytic leukemia

1. Peripheral blood monocytosis  $>1 \times 10^9/L$
2. Blasts  $<20\%$  in blood and marrow
3. No Ph chromosome or BCR/ABL fusion
4. Need two or more of the following:
  - Hemoglobin F increased for age
  - Immature granulocytes in peripheral blood
  - WBC count  $>10 \times 10^9/L$
  - Clonal chromosomal abnormality (e.g. monosomy 7)
  - GM-CSF hypersensitivity or myeloid progenitors *in vitro*

# Myelodysplastic/myeloproliferative disease, unclassifiable

1. Clinical and laboratory features of an MDS, with  $<20\%$  blasts in the blood or BM
2. Prominent myeloproliferative features
  - Platelet count  $\geq 600 \times 10^9/L$  with megakaryocytic proliferation
  - WBC  $\geq 13 \times 10^9/L$  with or without splenomegaly
3. No prior history of CMPD or MDS, no history or recent cytotoxic therapy or growth factors (mimic MDS/MPD features), no Ph chromosome or BCR/ABL fusion gene, no 5q-, no abnormalities of chromosome 3q21-26

# Chronic myeloproliferative diseases

- Clonal blood cell disorders characterised by proliferation in the bone marrow of one or more of the myeloid (e.g. erythroid, granulocytic, megakaryocytic) lineages
- Increased numbers of granulocytes, red blood cells or platelets in the blood
- Splenomegaly, hepatomegaly
- Any can result in bone marrow failure (fibrosis) or transformation to acute leukemia

# Chronic myeloproliferative diseases

- Any can result in bone marrow failure (due to fibrosis or ineffective hematopoiesis) or transformation to acute leukemia
- 10-19% blasts = accelerated phase
- $\geq 20\%$  blasts = acute leukemia

# Chronic myeloproliferative diseases

- Chronic myelogenous leukemia (Philadelphia chromosome, t(9;22)(q34;q11) positive, *BCR/ABL* positive) 9875/3
- Chronic neutrophilic leukemia 9963/3
- Chronic eosinophilic leukemia 9964/3
- Polycythemia vera 9950/3
- Chronic idiopathic myelofibrosis 9961/3
- Essential thrombocythemia 9962/3
- Chronic myeloproliferative disease, unclassifiable 9975/3

# Diagnosis of chronic myeloproliferative diseases

1. Rule out reactive causes of increased white blood cells, red blood cells or platelets
  - Chronicity
  - Splenomegaly
  - Presence or absence of infection, drugs, hypoxemia
2. Rule out CML with cytogenetics, or another molecular study for the *BCR/ABL* fusion

# Diagnosis of Chronic myeloproliferative diseases

3. Determine if there are features specific to any one disorder
  - Increased red cell mass (PV)
  - Megakaryocytic proliferation with fibrosis (CIM)
  - Increased platelets with proliferation of large megakaryocytes (ET)

# Chronic myelogenous leukemia (CML)

- The most straightforward diagnosis.
- Consistently associated with the Philadelphia chromosome, *BCR/ABL* fusion
- Chronic phase
- Accelerated phase
  - Blasts 10-19% of WBC in blood or BM, blood basophils  $\geq 20\%$ , persistent thrombocytopenia or thrombocytosis, increasing spleen size and WBC count, cytogenetic evidence of clonal evolution
- Blast phase
  - Blasts  $\geq 20\%$  in blood or BM, extramedullary blast proliferation, large foci or clusters of blasts in the bone marrow biopsy

# Chronic neutrophilic leukemia (CNL)

- All steps outlined previously
- Peripheral blood leukocytosis  $\geq 25 \times 10^9/L$ 
  - Neutrophils and bands  $> 80\%$  of WBC
  - Immature granulocytes  $< 10\%$  of WBC
  - Myeloblasts  $< 1\%$  of WBC
- Hypercellular bone marrow biopsy
  - Increased neutrophilic granulocytes
  - Myeloblasts  $< 5\%$
  - Normal neutrophilic maturation

# Chronic eosinophilic leukemia (hypereosinophilic syndrome, CEL)

- All steps outlined previously (exclude reactive, infectious and neoplastic causes)
- Persistent eosinophilia  $\geq 1.5 \times 10^9/L$  in the blood
- Increased eosinophils in bone marrow
- Myeloblasts  $< 20\%$  in blood or bone marrow

# Polycythemia vera (PV)

*Synonym: Polycythemia rubra vera*

1. Elevated RBC mass >25% above mean normal predicted value, or hemoglobin >18.5g/dL in men, 16.5 g/dL in women (=Polycythemia)
2. No cause of secondary erythrocytosis
  - Absence of familial erythrocytosis
  - No elevation of erythropoietin (EPO) due to:
    - Hypoxia
    - Abnormal hemoglobin
    - Truncated EPO receptor
    - Inappropriate EPO production by tumor, or exogenous EPO administration

# Polycythemia vera (PV)

Also need for diagnosis:

1. One of the following

- Splenomegaly
- Clonal genetic abnormality other than Ph chromosome
- Endogenous erythroid colony formation in vitro

2. Or two of the following

- Thrombocytosis  $>400 \times 10^9/L$
- WBC  $>12 \times 10^9/L$
- Hypercellular bone marrow biopsy with prominent erythroid and megakaryocytic proliferation
- Low serum EPO level

# Chronic idiopathic myelofibrosis (CIM)

Synonyms: Agnogenic myeloid metaplasia,  
Myelosclerosis with myeloid metaplasia, chronic  
granulocytic-megakaryocytic myelosis

Diagnosis:

- All steps outlined previously
- No specific criteria required by the WHO for diagnosis
- Characteristic changes in prefibrotic and fibrotic stages
- Prefibrotic phase:
  - Mild anemia, mild to moderate leukocytosis, mild to marked thrombocytosis

+/ leukoerythroblastosis on peripheral smear

# Chronic idiopathic myelofibrosis (CIM)

## Diagnosis:

- Prefibrotic phase (up to 30% of patients):
  - Present with splenomegaly, or an abnormal CBC (mild anemia, mild to moderate leukocytosis, mild to marked thrombocytosis)
  - +/- leukoerythroblastosis on peripheral smear
  - Hypercellular bone marrow with neutrophilic proliferation, megakaryocytic proliferation and minimal reticulin fibrosis

# Chronic idiopathic myelofibrosis (CIM)

## Diagnosis:

- Fibrotic phase (70-80% of patients):
  - Present with hepatosplenomegaly, and anemia
  - Leukoerythroblastosis on peripheral smear
  - Hypocellular bone marrow with fibrosis, dilated sinuses, prominent megakaryocytic proliferation and atypia, osteosclerosis

# Essential thrombocythemia (ET)

*Synonyms: Primary thrombocytosis, idiopathic thrombocytosis, hemorrhagic thrombocythemia*

- All steps outlined previously
- Sustained platelet count  $>600 \times 10^9/L$
- Bone marrow biopsy showing proliferation of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes

# Chronic myeloproliferative disease, unclassifiable (CMPD, U)

- Definite clinical, laboratory and morphologic features of a myeloproliferative disease, but fail to meet criteria specific for any CMPD entity, or have overlapping features
- Usually one of two categories:
  1. Initial stages of PV, CIMF, or ET in which characteristic features are not fully developed
  2. Late stage, advanced disease in which pronounced myelofibrosis, osteosclerosis, or transformation to acute leukemia obscures the underlying disorder.

# The future of CMPD classification

- If it could only all be as easy as CML.
- Overlap between the various entities makes classification difficult.
- Why split them?
  - Prognostic significance: ET=more indolent, usually does not progress to fibrosis
  - JAK2 mutation status may provide a new basis for classification, but the data is currently limited