CASE 2

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CASE HISTORY

- 64 year old Hispanic male with thrombocytosis
- Physical exam was normal
BLOOD COUNT

- CBC
  - WBC 10.8 K/mm^3
  - RBC 4.96 M/mm^3
  - HGB 15.2 g/dL
  - HCT 47.7%
  - MCV 96.2 fL
  - MCH 30.6 pg
  - MCHC 31.8 g/dL
  - RDW 17.4%
  - PLT 658 K/mm^3
  - MPV 7.1 fL

- WBC Differential
  - Segs 91%
  - Lymphs 5%
  - Monos 1%
  - Eos 1%
  - Basos 2%
Peripheral Blood
BM biopsy
Differential Diagnoses

- Essential thrombocythemia
- Polycythemia vera
- Chronic idiopathic myelofibrosis
- Reactive thrombocytosis
Janus kinase 2 (JAK2) and Myeloproliferative Diseases
JAK2

- Cytoplasmic tyrosine kinase protein
- Named after the Roman god with two faces
- JAK contains two homologous kinase domains
JAK-STAT pathway

Cytokine receptor

JAK inhibitor

JAK

STAT

STAT dimer

Nucleus

Target genes

Transcription
JAK2 Mutation

- It is present in nearly all (90%) of patients with PV
- 30-50% of patients with ET or CIMF.
Additional Data for the Case

• JAK2 mutation was detected on the bone marrow aspirate.

Differential Diagnoses

ET  PV  CIMF
2008 Proposed WHO Classification

- MPD renamed to Myeloproliferative Neoplasms (MPN)
- Chronic idiopathic myelofibrosis (CIMF) renamed primary myelofibrosis (PMF)
- JAK2 mutation
- New diagnostic criteria for PV, ET, PMF/CIMF
Proposed WHO Criteria for Essential Thrombocythemia

- Sustained platelet count $\geq 450 \times 10^9/L$
- JAK2 mutation present
- Increased large megakaryocytes
- PV, PMF, CML, MDS ruled out
- No reactive thrombocytosis
Final Diagnosis

- Essential Thrombocytopenia
Proposed WHO Criteria for Polycythemia Vera

Major criteria

• Hb>18.5g/dL in men, 16.5g/dL in women

• Presence of JAK2 or other functionally similar mutation
Proposed WHO Criteria for Polycythemia Vera

Minor Criteria

- Hypercellular BM with trilineage growth
- Decreased serum erythropoietin level
- Endogenous *in vitro* erythroid colony formation
Peripheral blood
BM smear
Proposed WHO Criteria for Primary Myelofibrosis

Major Criteria

- JAK2 or other clonal marker present
- Rule out PV, CML, and MDS
- Reticulin fibrosis
Proposed WHO Criteria for Primary Myelofibrosis

**Major criteria**
- Megakaryocytic proliferation with atypia.
- Hypercellular BM with granulocytic proliferation and decreased erythropoiesis.
Proposed WHO Criteria for PMF/CIMF

Minor criteria

• Increase in serum LDH
• Leukoerythroblastosis
• Anemia
• Splenomegaly
Peripheral blood
BM Findings in Reactive Thrombocytosis (RT)

- Normal cellularity
- Dispersed small to medium-sized megakaryocytes
Cellularity

- Increased
  - PV/CIMF
    - Megakaryocytes
      - Small to giant, hyper-lobulated
        - PV
      - Maturation defects and apoptotic nuclei
        - CIMF
    - ET/RT
      - Normal
        - ET
          - Small to medium
          - RT
MPD Diagnostic Algorithm

BM biopsy, cytogenetic/molecular studies

\[ \text{JAK2}(-) \] \quad \downarrow \quad \text{Other causes} \quad \downarrow

\[ \text{Jak2} (+) \] \quad \downarrow \quad \text{MPD} \quad \downarrow

Study morphology to differentiate MPDs