Myeloproliferative Neoplasms: A Case-Based Approach

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Objectives

• Recognize the typical laboratory findings and peripheral blood smear morphology for myeloproliferative neoplasms
• Be familiar with expected bone marrow aspirate and biopsy morphologic findings in myeloproliferative neoplasms
• Understand the role of molecular testing in the diagnosis of myeloproliferative neoplasms

Myeloproliferative Neoplasms

• Clonal proliferation of bone marrow cells resulting in increased production of mature cells
• No significant dysplasia
• Strong association with splenomegaly at presentation

Disclosures

• No conflicts of interests regarding the topic being presented

Myeloproliferative Neoplasms

• Chronic myeloid leukemia, BCR-ABL1-positive
• Chronic neutrophilic leukemia
• Polycythemia vera
• Primary myelofibrosis
• Essential thrombocythemia
• Chronic eosinophilic leukemia, NOS
• Myeloproliferative neoplasm, unclassifiable

Myeloproliferative Neoplasms

• Diagnosis often requires integration of multiple data points
  – Bone marrow morphology
  – Clinical data
  – Laboratory data
• Tendency to progress to eventual bone marrow failure or acute leukemia
Case 1

- 86 year-old woman
- Clinical history of diverticulitis, duodenal ulcers, and gastrointestinal bleeding
- Presented with one week history of abdominal pain and nausea
- Physical exam unremarkable

Case 1

- WBC: 12.5 k/cumm
  - Neutrophils: 64%
  - Lymphocytes: 18%
  - Monocytes: 9%
  - Eosinophils: 6%
  - Basophils: 3%
- Hemoglobin: 19.4 g/dL
  - MCV: 94 fL
  - RDW: 14.4%
- Platelets: 690 k/cumm
- Erythropoietin: 2.2 mIU/mL

Case 1

- Flow cytometry of the peripheral blood and bone marrow:
  - No immunophenotypic evidence of lymphoma or leukemia

Case 1

- Bone marrow aspirate differential:
  - Blasts: 1%
  - Promyelocytes: 5%
  - Myelocytes: 17%
  - Metamyelocytes: 5%
  - Bands: 14%
  - Polys: 25%
  - Lymphocytes: 6%
  - Monocytes: 2%
  - Eosinophils: 2%
  - Nucleated RBCs: 22%
Case 1

- JAK2 V617F mutation detected by both PCR and myeloid NGS
- Final Diagnosis: Polycythemia vera

Polycythemia Vera

- Chronic myeloproliferative neoplasm characterized by increased red blood cell production independent of mechanisms that normally regulate erythropoiesis

Polycythemia Vera

- 0.84 cases per 100,000 people/year
- Median age of diagnosis is 60 years
- Pediatric cases are rare
- Slight male predominance
Polycythemia Vera

- Major Criteria
  - Elevated hemoglobin concentration (> 16.5 g/dL for men, >16.0 g/dL for women)
  - Bone marrow biopsy showing age-adjusted hypercellularity with panmyelosis
  - Presence of JAK2 V617F or JAK2 exon 12 mutation
- Minor Criteria
  - Subnormal serum erythropoietin level

- Two phases clinically
  - Polycythemic phase
    - Increased red blood cell mass
    - Clinically associated with pruritus (post-shower), thrombosis, erythromelalgia
  - Spent phase (post polycythemia vera myelofibrosis)
    - Fibrosis
    - Cytopenias
    - Extramedullary hematopoiesis

- Good prognosis (decades range)
- Possible evolution to myelodysplastic syndrome or leukemia (2-3% of cases)
- Mortality primarily due to bone marrow failure or progression to leukemia
- Treatment consists of therapeutic phlebotomy and cytoreductive agents (primarily hydroxyurea)
  - May utilize JAK2 inhibitors (e.g. ruxolitinib) if inadequate response or intolerance

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Polycythemia Vera

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Case 2

- 59 year-old man
- Clinical history of alcohol abuse, hypertension, and type 2 diabetes
- Presented with one month history of weight loss and night sweats
- Physical exam remarkable for splenomegaly palpable 5 cm below the costal margin

- WBC: 461.4 k/cumm
  - Blasts: 1%
  - Promyelocytes: 6%
  - Myelocytes: 22%
  - Metamyelocytes: 11%
  - Bands: 13%
  - Neutrophils: 37%
  - Lymphocytes: 1%
  - Monocytes: 3%
  - Eosinophils: 4%
  - Basophils: 5%

- Hemoglobin: 10.6 g/dL
  - MCV: 79 fl.
  - RDW: 19.2%
  - Platelets: 498 k/cumm

- Flow cytometry of the peripheral blood:
  - No immunophenotypic evidence of lymphoma or leukemia

- Bone marrow biopsy touch preparations differential:
  - Blasts: 5%
  - Promyelocytes: 3%
  - Myelocytes: 24%
  - Metamyelocytes: 12%
  - Bands: 20%
  - Polys: 26%
  - Lymphocytes: 1%
  - Eosinophils: 5%
  - Basophils: 2%
  - Nucleated RBCs: 2%
Case 2

- Peripheral blood and bone marrow cytogenetics:
  - 46,XY,t(9;22)(q34;q11.2)
- Peripheral Blood FISH:
  - Positive for BCR-ABL1 Fusion
- Peripheral Blood BCR-ABL1 PCR:
  - p210 transcripts: 82.092%
  - p190 transcripts: 0.076%
- Final Diagnosis: Chronic myeloid leukemia

Chronic Myeloid Leukemia

- Myeloproliferative neoplasm secondary to a BCR-ABL1 fusion gene in a hematopoietic stem cell in which granulocytes are the major proliferative component

- Most common myeloproliferative neoplasm
- 1.5 cases per 100,000 people/year
- Represents 15-20% of all leukemia diagnoses
- Median age of diagnosis is 67 years and correlates strongly with age
- Pediatric cases are rare
- Slight male predominance

- No WHO defined criteria for diagnosis
- Detection of BCR-ABL1 fusion gene in the appropriate clinical and laboratory settings

- p210 – Most commonly detected in CML and occasionally in ALL or AML
- p190 – Common in B-cell ALL and occasionally in AML but rarely in CML (typically with monocytosis)
- p230 – CML with neutrophilic maturation or conspicuous thrombocytosis
Chronic Myeloid Leukemia

BCR-ABL1 Fusion Protein

Constitutive Tyrosine Kinase Activity

Activation of Intracellular Signaling Pathways

Transcription of Genes Related to Proliferation and Survival

Chronic Myeloid Leukemia

- Triphasic disease
  - Chronic phase (>90% of patients)
  - Accelerated phase
  - Blast phase

Chronic Myeloid Leukemia

- Chronic phase, clinical and laboratory findings
  - 50% discovered when asymptomatic
  - Fatigue, malaise, weight loss, night sweats, splenomegaly
  - Patients typically present with marked leukocytosis:
    - Increased myeloid cells at all stages of maturation
    - Basophilia and eosinophilia
    - Absolute monocytosis
    - Thrombocytosis
    - Splenomegaly

Chronic Myeloid Leukemia

- Chronic phase, bone marrow
  - Hypercellular with marked granulocytic proliferation similar to the peripheral blood
  - Markedly increased myeloid to erythroid ratio
  - Normal to increased megakaryocytes with “dwarf” morphology
  - Histiocytes
  - Reticulin fibrosis in 30-40% of cases

Chronic Myeloid Leukemia

- Accelerated phase
  - 10-19% blasts in the peripheral blood or bone marrow
  - Persistent thrombocytopenia
  - ≥20% basophils in the peripheral blood
  - Additional chromosomal abnormalities
  - Persistent or increasing WBC count, unresponsive to therapy
  - Persistent or increasing splenomegaly, unresponsive to therapy
  - Persistent thrombocytosis, unresponsive to therapy

Chronic Myeloid Leukemia

- Blast phase
  - ≥20% blasts in the blood or bone marrow
  - Extramedullary proliferation of blasts
Chronic Myeloid Leukemia

- 10 year survival rate of 80-90% with current therapy
- Without therapy, progress to acute leukemia in 3 to 5 years
- Mortality related to progression to acute leukemia
- Presentation in blast phase is a poor prognostic marker
- Tyrosine kinase inhibitors are the mainstay of treatment

Case 3

- 50 year-old man
- Clinical history of chronic portal venous thrombosis following abdominal surgery
- Presented with upper abdominal pain
- Physical exam remarkable for massive splenomegaly

Case 3

- WBC: 23.4 k/cumm
  - Myelocytes: 2%
  - Bands: 1%
  - Neutrophils: 78%
  - Lymphocytes: 4%
  - Monocytes: 2%
  - Eosinophils: 10%
  - Basophils: 1%

- Hemoglobin: 11.6 g/dL
- MCV: 69 fL
- RDW: 25.3%
- Platelets: 286 k/cumm

Case 3

- Flow cytometry of the peripheral blood and bone marrow:
  - No immunophenotypic evidence of lymphoma or leukemia
Case 3

- Bone marrow aspirate differential:
  - Blasts: 3%
  - Promyelocytes: 7%
  - Myelocytes: 11%
  - Metamyelocytes: 13%
  - Bands: 12%
  - Polys: 18%
  - Lymphocytes: 3%
  - Eosinophils: 7%
  - Nucleated RBCs: 25%
Case 3

- JAK2 V617F mutation detected by myeloid NGS
- Final diagnosis: Primary myelofibrosis

Primary Myelofibrosis

- Clonal myeloproliferative neoplasm characterized by a proliferation of predominantly abnormal megakaryocytes and granulocytes associated with bone marrow fibrosis and extramedullary hematopoiesis

- 0.47 cases per 100,000 people/year
- Median age of diagnosis is 65 years
- Rare in pediatric population
- No sex predilection

Primary Myelofibrosis

- Two stages
  - Prefibrotic/early (30-50%)  
    - Often asymptomatic (30%)
    - Palpable splenomegaly
    - Anemia, leukocytosis, or thrombocytosis
  - Overt fibrotic  
    - Fatigue, dyspnea, weight loss, night sweats, fever, cachexia
    - Palpable splenomegaly
    - Anemia, leukoerythroblastosis, thrombocytopenia
    - Increased LDH

Primary Myelofibrosis

- Prefibrotic/early stage
  - Major criteria
    - Megakaryocytic proliferation and atypia, without significant reticulin fibrosis (grade 0–1), accompanied by bone marrow hypercellularity, granulocytic proliferation, and decreased erythropoiesis.
    - Criteria for BCR-ABL1-positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndrome, and other myeloid neoplasms are not met
    - Evidence of clonality
      - JAK2 (50-60%), CALR (24%), or MPL (8%) mutation
    - Other clonal markers
    - Absence of reactive conditions
  - Minor criteria
    - Anemia
    - Leukocytosis
    - Splenomegaly
    - Increased LDH
Primary Myelofibrosis

- Overt fibrotic stage
  - Major criteria
    - Megakaryocytic hyperplasia and atypia with significant reticulin and/or collagen fibrosis (grade 2–3)
    - Criteria for BCR-ABL1-positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndromes, and other myeloid neoplasms are not met
    - Evidence of clonality
      - JAK2 (50–60%), CALR (24%), or MPL (8%) mutations
      - Other clonal markers
      - Absence of reactive conditions
  - Minor criteria
    - Anemia
    - Leukocytosis
    - Splenomegaly
    - Increased LDH
    - Leukocytosis
  - Associated with accelerated phase (10–19% blasts) and blast transformation (≥20%)
    - Progression to blast phase seen in 5–30% of patients

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Primary Myelofibrosis

- Highly variable prognosis from months to years
  - Dependent on stage at time of presentation
  - 72% 10 year survival for those presenting in the prefibrotic stage
  - 3-7 years for patients presenting in overt fibrotic stage
- Mortality related to bone marrow failure or progression to acute leukemia
- Treatment with JAK2 inhibitors (e.g. ruxolitinib) or allogeneic hematopoietic stem cell transplant

Case 4

- 81 year-old man
- Clinical history of hypertension and renal insufficiency
- Bilateral knee replacement one year prior with associated anemia, now corrected
- Routine testing incidentally revealed increased platelet count
- Physical exam unremarkable

Case 4

- WBC: 9.7 k/cumm
  - Neutrophils: 74%
  - Lymphocytes: 16%
  - Monocytes: 8%
  - Eosinophils: 1%
  - Basophils: 1%
- Hemoglobin: 16.5 g/dL
  - MCV: 95 fl
  - RDW: 13.9%
- Platelets: 587 k/cumm

Case 4

- Flow cytometry of the bone marrow:
  - No immunophenotypic evidence of lymphoma or leukemia

Case 4

- Bone marrow aspirate differential:
  - Blasts: 1%
  - Promyelocytes: 4%
  - Myelocytes: 15%
  - Metamyelocytes: 2%
  - Bands: 13%
  - Polys: 20%
  - Lymphocytes: 12%
  - Eosinophils: 2%
  - Nucleated RBCs: 25%
Case 4

- JAK2 V617F mutation detected by both PCR and myeloid NGS
- Final diagnosis: Essential thrombocythemia

Essential Thrombocythemia

- Chronic myeloproliferative neoplasm primarily involving the megakaryocytic lineage characterized by sustained thrombocytosis and increased numbers of large, mature megakaryocytes in the bone marrow
Essential Thrombocytemia

- 1.03 cases per 100,000 people/year
- Most cases diagnosed in patients 50-60 years of age
  - Smaller incidence around 30 years of age
- Slight female predilection

Essential Thrombocytemia

- Major criteria
  - Thrombocytosis
  - Bone marrow with increased numbers of mature megakaryocytes with hyperlobulated nuclei and no significant fibrosis or increased in granulopoiesis or erythropoiesis
  - Criteria for BCR-ABL1-positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, and other myeloid neoplasms are not met
  - JAK2 (50-60%), CALR (30%), or MPL (3%) mutation
- Minor criteria
  - Presence of a clonal marker
  - Absence of evidence for reactive thrombocytosis

Essential Thrombocytemia

- >50% of cases are discovered incidentally
- Remaining cases usually present with a manifestation of vascular occlusion or hemorrhage
  - Microvascular occlusion
    - Transient ischemic attacks, digital ischemia, paraesthesias, or gangrene
  - Thrombosis of major vasculature
    - Budd-Chiari syndrome
  - Hemorrhage typically in mucosal sites
- Splenomegaly in only 15-20% of cases

Essential Thrombocytemia

- Indolent disorder characterized by long symptom-free intervals interrupted by life-threatening thromboembolic or hemorrhagic events
- Median survival of 10-15 years
- 10% progress to post-essential thrombocytemia myelofibrosis
- <5% progress to acute myeloid leukemia or myelodysplastic syndrome
- Treatment consists of aspirin or cytoreductive agents (primarily hydroxyurea)

Summary

- Myeloproliferative neoplasms have significant overlap
  - Clinical
  - Laboratory
  - Morphology
- Integration of all available data are necessary to arrive at the appropriate diagnosis

References


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