Myelodysplasias and Myeloproliferative disorders
Diagnosis, treatment, and prognosis

MDS
- Hematologic conditions characterized by chronic cytopenias (anemia, neutropenia, thrombocytopenia) accompanied by abnormal cellular maturation
- Risk for anemia, infection, and bleeding, progression to acute leukemia (which is often refractory to standard treatment)

MDS (myelodysplasia)
- Is a malignant clonal stem cell disease
- Characterized by dysplasia and ineffective blood cell production
- Prevalence is about 4/100,000
- Incidence increases with increasing age (incidence of 89/100,000 in age over 80)
- Median age of onset is 65, with male predominance
- Onset <age 50: rare, can be seen in treatment related MDS
Risk factors

- Heritable predisposition
  - Constitutional genetic disorders
    - Down syndrome (trisomy 21)
    - Trisomy 8 mosaicism
    - Familial monosomy 7
    - Neurofibromatosis 1
    - Germ cell tumors (embryonal dysgenesis)
    - Congenital neutropenia (Kostmann's or Shwachman-Diamond syndrome)
    - DNA repair deficiencies
      - Fanconi's anemia
      - Ataxia telangiectasia
      - Bloom's syndrome
      - Xeroderma pigmentosum

- Acquired
  - Senescence
    - Mutagen exposure
    - Genotoxic therapy
      - Alkylators (chlorambucil, cytoxan, dacarbazine, ifosfamide)
      - Topoisomerase II interactive agents (etoposide)
      - -emitters (32p)
        - Hematopoietic cell transplantation
        - Environmental/occupational (eg, benzene)
        - Tobacco
        - Aplastic anemia
        - Paroxysmal nocturnal hemoglobinuria (PNH)
        - Polycythemia vera

Clinical presentation

- Signs & symptoms
  - Non-specific, routine lab testing may show cytopenia
  - Symptoms may be seen with severe cytopenias
  - Easy bruising or bleeding
  - Frequent infections
  - Systemic “B” symptoms like fevers/night sweats/weight loss occur late in the course
Infection in MDS

- Due to neutropenia or granulocyte dysfunction
- Bacterial infections/skin infections most common
- Main cause of death

Skin findings

- Uncommon
- Sweet’s syndrome (acute febrile neutrophilic dermatosis)
  - Usually heralds transformation to acute leukemia
  - acute onset of fever, leukocytosis, and erythematous plaques infiltrated by neutrophils
  - Skin lesions may be plaques, pustules, nodules, ulceration
- Granulocytic sarcoma/chloroma

Sweet’s syndrome-associated conditions

- Malignancies seen in 20-25% (MDS, AML, GU/GI/breast cancers more rarely)
- Bacterial infections — vaccinations, streptococcus, mycobacterium, Yersinia, typhus, salmonella
- Viral infections — cytomegalovirus, chronic active hepatitis, HIV
- Drugs — lithium, furosemide, hydralazine, oral contraceptives, minocycline, gleevac and bactrim.
- Autoimmune and collagen vascular diseases — rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, Hashimoto thyroiditis, Sjögren’s syndrome, Behcet’s disease
- Inflammatory bowel disease — Crohn’s disease, ulcerative colitis
- Other — pregnancy, complement deficiency, subacute necrotizing lymphadenitis, and Poem’s syndrome
• Erythematous annular plaque lesions

Physical findings
• Typically due to cytopenias
• Bruising, pallor
• Organomegaly rare except in CMML

Lab findings
• Red cells
  – Anemia with inappropriately low reticulocyte response
  – Normocytic or macrocytic RBCs
  – Basophilic stippling, Howell Jolly bodies, nucleated RBCs
• WBCs (neutrophils)
  – 50% will have leukopenia
  – Pseudo Pelger-Huet neutrophils (reduced segmentation)
  – Decreased granulation of neutrophils
  – Early precursors may be seen in peripheral blood
  – Auer rods in myeloblasts
  – Monocytosis

Peripheral blood smear from a patient with refractory anemia with excess blasts (RAEB) shows a neutrophil with a bilobed pseudo-Pelger-Huet (Pelgeroid) nucleus. The two lobes are connected by a thin strand (arrow) giving a “pince-nez” appearance. These nuclei look identical to those seen in the inherited Pelger-Huet anomaly. This neutrophil also has markedly reduced granulation, a finding commonly seen in the myelodysplastic syndromes. From Brunner, RD, Mohanna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle). Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology

Auer rods (seen in RAEB-t)

Rod-like conglomeration of granules in the cytoplasm within a blast cell (pathognomonic of acute myeloid leukemia)
• Platelets
  – Thrombocytopenia in 25%
  – Thrombocytosis
    • 5q- syndrome
    • 3q21q26 syndrome
    • Refractory anemia with ringed sideroblasts with thrombocytosis

• Lymphocytes & immunoglobulins
  – Lymphopenia not common, since lymphocytes are not from the malignant clone
  – Variabilities in IGs may be seen:
    hypogammaglobulinemia, polyclonal hypergammaglobulinemia, monoclonal gammopathy

Bone marrow findings
• Hypercellular (hypocellular marrow classically seen in therapy related MDS)
• Single or multi-lineage dysplasia
• Basophilia or eosinophilia
• Abnormal megakaryocytes with clustering
Bone Marrow findings

• Classic: peripheral pancytopenia despite the presence of a hypercellular bone marrow reflects premature cell loss via intramedullary cell death (apoptosis)
• RBCs: dyserythropoietic features in precursors (distorted nuclear and cytoplasmic maturation, erythroid hyperplasia with megaloblastoid features

Bone marrow findings

An increase in mast cells, plasmacytes, and histiocytes
Bone marrow eosinophilia (>5.0 percent), bone marrow basophilia (>1.0 percent), or both
Hypocellularity is uncommon (seen with therapy-related MDS)

• Pathologic sideroblasts containing more than five iron granules per cell may be evident on bone marrow specimens stained for the presence of iron
• Sideroblasts in which iron granules occupy more than one-third of the nuclear rim are termed "ringed" sideroblasts
Ringed sideroblasts

Myelodysplastic syndrome with abnormal megakaryocytic maturation
Bone marrow aspirate from a patient with myelodysplastic syndrome. The
megakaryocytes are abnormal, with multiple small lobes seemingly
disconnected from each other ("pawn ball" changes, arrows). (Wright-Giemsa).
Courtesy of David S Rosenthal, MD.

Other findings

MRI (of femur or hip) may show an unexpected inhomogeneous or diffuse
cellular pattern (this should not be used as a screening tool)
### WHO Classification

**Refractory Anemia**
- <5% bone marrow blasts
- Erythroid dysplasia only
- <1% peripheral blasts
- No monocytosis, ringed sideroblasts or Auer rods

**Refractory anemia with ringed sideroblasts**
- >15 percent ringed sideroblasts.

**Refractory cytopenia with multilineage dysplasia**
- <5 percent BM blasts
- Severe dysplasia in two or more cell lines

**Refractory anemia with multilineage dysplasia and ringed sideroblasts**
- >15% ringed sideroblasts

**Refractory anemia with excess blasts**
- Characterized by 5 to 19 percent BM blasts
  - RAEB 15% blasts
  - RAEB 210% blasts
  - significant difference in prognosis between the two
Chronic myelomonocytic leukemia

- Up to 20 percent BM blasts
- <5 percent peripheral blasts, and peripheral monocyte count >1000/microL
- CMML has two subtypes:
  - WBC < 12,000/microL are considered to have MDS
  - WBC >12,000/microL, proliferative type of CMML (considered to have myeloproliferative disorder)

Refractory anemia with excess blasts in transformation/ evolving AML

- Was present in FAB classification (blasts 20-30%)
- In WHO (newer) classification, is evolving AML and treated as such

MDS with del(5q) "5q- syndrome"

- Anemia
- Normal to increased megakaryocytes with hypolobulated nuclei
- <5 percent blasts
- No Auer rods
- Platelets usually normal or increased
5q-syndrome

- Interstitial deletion of the long arm of chromosome 5
- Female predominance (7:3) with a median age at diagnosis of 68 years
- Transfusion-dependent anemia
- Low incidence of neutropenia, thrombocytopenia, infection, and bleeding
- Normal or increased platelet counts along with bone marrow hyperplasia of hypolobulated micromegakaryocytes
- Low incidence of transformation into acute leukemia (16 percent)

Subtype incidence

- Refractory anemia — 21 percent
- Refractory anemia with ringed sideroblasts — 17 percent
- Refractory anemia with excess blasts — 37 percent
- Refractory anemia with excess blasts in transformation — 12 percent
- Chronic myelomonocytic leukemia — 13 percent

Cytogenetics in MDS

- Survival is shorter in patients with abnormal karyotypes, particularly those with complex abnormalities
- Del(5q) or del(20q) more favorable
- Outcome is also poor in patients with a single defect involving chromosome 7
Prognosis

- Progression to AML in 22 to 35 percent
  - 5 to 15 percent in RA and RARS
  - 40 to 50 percent in RAEB and RAEB-T

Therapy related MDS

- Following alkylating agents and/or radiation therapy
  - Typically latent period of five to seven years
  - 50% evolve to AML within a median of six months
  - Median survival is only about eight months
  - Involvement of chromosomes 5 and/or 7
  - Increased risk of acute myeloid leukemia reported in aircrew, possibly in association with cosmic radiation

Following DNA topoisomerase II inhibitors

- Etoposide, tenoposide, mitoxantrone, doxorubicin
- Shorter latency period (about 30-34 months)
- Most present with leukemia, rarely with MDS
- More favorable response to intensive chemotherapy (for AML)
- Often involve the MLL gene at 11q23
Following immunosuppressive and growth factor therapy for aplastic anemia

- Acquisition of monosomy 7
- Concerns have been raised about possible effect from long term G-CSF use

Treatment: Goals

- Control of symptoms
- Improving quality of life and minimizing the side effects of therapy
- Decreasing progression to acute leukemia
- Improving overall survival

Risk stratification for treatment

- Age of patient
- Performance status
- Risk category, as defined by the IPSS (International prognosis scoring system)
IPSS

- Looks at number of blasts in marrow, karyotype, and number of cytopenias
- Good karyotypes: Normal, del (5q), del (20q)
  Poor: Complex (3 abnormalities); abnormal chromosome 7
  Intermediate: All others
- Less than 5% blasts good, 5-10% intermediate

Cytopenias:
- Red blood cells: Hgb <10 g/dL
- WBC: Absolute neutrophil count <1800/µL
- Platelet count <100,000/µL

Treatment

High intensity treatment: requires hospitalization, includes intensive combination chemotherapy/bone marrow transplantation

Low intensity treatment: outpatient treatments (hematopoietic growth factors, differentiation-inducing agents, biologic response modifiers, and low intensity chemotherapy)

Treatment

< 60 years of age with minimal symptoms and IPSS intermediate-2 or high risk categories (expected survival 0.3 to 1.8 years)
  Consider stem cell transplant in highly selected pts, otherwise newer differentiation agents
>60 years of age with good performance status (expected survival 0.4 to 5 years)
  – low intensity therapy in general
  – Supportive care

Treatment

• Growth factors
  – G CSF, GM CSF, Epo
    • In general, disappointing results
  – May be used
    • In neutropenic patients with antibiotic-resistant fever/infection
    • In combination with erythropoietin (sometimes will get an increase in counts temporarily)

Lenalidomide (Revlimid)

• Immunomodulatory and antiangiogenic actions via multiple mechanisms
• A thalidomide derivative without the neurologic toxicity of the parent compound
• Best responses in 5q- syndrome and low IPSS scores
• Restoration of a normal chromosome may be seen
LOW/INTERMEDIATE INTENSITY CHEMOTHERAPY

- Azacitidine (Vidaza): causes hypomethylation of DNA and direct cytotoxicity on abnormal bone marrow hematopoietic cells
  - phase III clinical trial (CALGB: 191 patients)
    - RR: 23 vs 0%
    - Median time to progression: 21 versus 13 months
    - QOL sig improved
    - no significant difference in overall survival (but was a crossover trial)
    - Approved for use in RA or RARS (if accompanied by neutropenia or thrombocytopenia, or requiring transfusions), RAEB, RAEB-T, and CMML

- Decitabine (Dacogen)
  - strongly inhibits DNA methylation, is capable of inducing cell differentiation
  - Phase II trials show improvement in blood counts and cytogenetic responses
  - FDA approved for previously treated, untreated, de novo, and secondary MDS of all FAB subtypes and intermediate-1, intermediate-2, and high-risk IPSS groups

Stem cell transplant

- Limited by donor availability and the advanced age of most patients
- Consider for patients <60 and with an HLA-matched sibling donor
- Transplant-related mortality and the relapse rate at five years are as high as 40 percent
Diagnosis

- Suspect in any elderly pt with unexplained cytopenia or monocytosis
- Evaluate cytopenias over time (obtain old records)
- Suspect in anemia with elevated MCV with no B12/folate deficiency or liver disease
- Suspect in pts with cytopenia and systemic symptoms (weight loss, night sweats; “B” symptoms)

Differential diagnosis

- B12/folate deficiency
- Aplastic anemia
- Myelofibrosis
- ETOH abuse with bone marrow recovery
- HIV infection
- Medications (valproic acid, ganciclovir, campath, cellcept)
- Copper deficiency/zinc excess

Myeloproliferative disorders
Myeloproliferative disorders

• Usually show increased myeloid cells in the peripheral blood
• Classified into "classic" and "atypical"
• Classic:
  – polycythemia vera
  – essential thrombocytosis
  – chronic myelogenous leukemia (CML)
  – chronic idiopathic myelofibrosis (AMM, agnogenic myeloid metaplasia).

Myeloproliferative disorders

• Atypical MPDs: (chronic myeloid disorders which are currently not classifiable as either MDS or classical MPD)
  – chronic myelomonocytic leukemia
  – juvenile myelomonocytic leukemia
  – systemic mastocytosis
  – hypereosinophilic syndrome
  – chronic neutrophilic leukemia
  – chronic eosinophilic leukemia
  – chronic basophilic leukemia and unclassified MPD.

Etiology

• Neoplastic clone of a multipotent stem cell which leads to increased hematopoiesis
Complications

• Propensity to transform into acute myeloid leukemia
  – Highest for CML (greater than 90 percent in the absence of effective therapy)
  – Least for ET (less than 5 percent)
  – PV have 10 and 25 percent chance of transforming into a myelofibrotic stage at 10 and 25 years of follow up, respectively

Complications: Thrombotic

• Arterial and venous thromboses and microcirculatory disorders such as erythromelalgia (burning pain in the feet or hands accompanied by erythema, pallor, or cyanosis, in the presence of palpable pulses)
• Visual and neurological symptoms
• Most often in PV and ET

Complications: Hemorrhagic

• Bleeding episodes usually mild
• Spontaneous bleeding can occur with high platelet counts
• Both quantitative and qualitative changes in platelet function may contribute
Symptoms

- Fatigue — 81 percent
- Pruritus — 52 percent
- Night sweats — 49 percent
- Bone pain — 44 percent
- Fever — 14 percent
- Weight loss — 13 percent

CML

- An acquired abnormality where one chromosome breaks off and attaches to another chromosome (results in an abnormally short chromosome, the Philadelphia chromosome)
- Two genes (BCR and ABL) fuse into one gene, BCR-ABL
- BCR-ABL gene causes bone marrow cells to produce an abnormal enzyme (tyrosine kinase) which stimulates abnormal growth of WBCs

CML

- Accounts for approximately 15 to 20 percent of cases of leukemia in adults
- Slight male predominance
- Median age at presentation is about 50 years
- Uncontrolled production of maturing granulocytes
Diagnosis: symptoms

- Up to 50 percent are asymptomatic
- Systemic symptoms ("B" symptoms: fatigue, malaise, weight loss, night sweats), abdominal fullness, and bleeding episodes
- Abdominal discomfort and early satiety due to splenomegaly
- Bony pain (especially sternal)
- Gouty arthritis

Diagnosis: Clinical

- Splenomegaly (50 to 75% of patients)
- Anemia
- WBC over 100,000
- Thrombocytosis around 600 to 700,000
- Elevated uric acid
- Peripheral smear: presence of virtually all cells of the neutrophilic series
- Low or absent level of alkaline phosphatase activity in circulating neutrophils (LAP)
• Myeloblasts

• Metamyelocyte

• Normal band
Bone marrow biopsy

- In chronic phase shows granulocytic hyperplasia (nondiagnostic)
- Increase in reticulin fibrosis and vascularity
- Cytogenetics should be done and will show Ph chromosome (t 9;22)

• Diagnosis of CML is imperative on demonstration of the Philadelphia chromosome by cytogenetics of the underlying t(9;22) translocation, or finding the BCR-ABL fusion mRNA or the Bcr-Abl protein
Phases of CML

- Chronic Phase: < 5 percent blasts
  - 85 percent of patients are in the chronic phase when initially diagnosed
  - This phase generally lasts several years and is controllable with oral chemotherapy medications (in the past, hydrea)

Accelerated phase CML

- Maturation of WBC’s progressively impaired
  - 5 to 30 percent blast cells in the blood and bone marrow
  - More difficult to control with medications
  - New mutations that develop in the blast cells
CML: blast phase

- More than 30 percent blast cells in the blood or bone marrow
- Before recent advances in treatment, blast crisis typically occurred four to five years after diagnosis and was unresponsive to treatment and led to death within a few months

Treatment options

- Stem cell transplantation (bone marrow transplantation)
- Oral tyrosine kinase inhibitors such as imatinib (Gleevec) or dasatinib (Sprycel)
- Interferon alpha with or without cytarabine (now rarely used)
- Hydroxyurea (was a primary treatment in past, now used rarely)

- Primary goal of treatment is to markedly reduce or eliminate the cells with the abnormal Philadelphia chromosome (cytogenetic response)
- Hematological response is return of blood counts to normal (secondary goal)
- Molecular response: lack of BCR-ABL proteins by molecular testing (gold standard)
Stem cell transplantation

- Was considered the best treatment for CML in past, now unclear
- Donor may be the patient (Autologous transplant) or identical twin (Syngeneic transplant)
- Allogeneic transplants come from a relative or from an unrelated donor

In the past, transplantation within the first year of chronic phase resulted in the best outcomes.
- Not clear in patients treated with imatinib, if longer delays to transplantation compromise the outcome

Related donors

- 50 to 75 percent of patients with CML transplanted in the first or second chronic phase of their disease achieve long-term remissions
- Disease-free survival:
  - 30 to 40 percent in patients transplanted in the accelerated phase
  - 10 to 20 percent in patients transplanted in blastic phase. (Chemotherapy or Gleevec prior to transplantation often used)
Age and transplant/related donors

- Patient age has a major influence on the outcome after transplantation with cells from a sibling donor
- < age 50 who undergo transplant during first year of diagnosis: 5 yr DFS is 70 to 85 percent

Matched unrelated donors

- Search through the National Marrow Donor Program and other donor agencies
- Less successful in certain minority populations that are under-represented within the donor programs.
- Estimated five year survival was 74 percent in patients who were 50 years of age or younger

Autologous

- Patient's own hematopoietic cells are removed, stored and purified, chemotherapy is given to reduce the number of abnormal cells, and then stored cells are re-transplanted
  - Generally not effective in CML
- Syngeneic: has been associated with a higher risk of disease relapse compared to a matched related or unrelated donor in CML
Risks of transplant

- Toxicity: life-threatening bacterial, viral, or fungal infection, anemia, and bleeding
- Failure to engraft
- Graft-versus-host disease (GVHD)
  - Major cause of death after transplant
  - Requires treatment with antirejection medications (tacrolimus, cyclosporine, prednisone)

Relapse after transplant

- Treated with imatinib or dasatinib or with infusions of leukocytes (DLI) from the original donor, with the hope of mounting a graft-versus-tumor effect

Deciding between Transplantation and Imatinib

- No RCTs comparing the two in newly diagnosed CML
- Allogeneic HCT remains the only treatment approach that is known to cure CML
- Younger patients in the chronic phase who have a suitably matched sibling donor should consider transplant
- Patients prefer Gleevec as initial treatment
- Recent expert panel recommended gleevec as 1st treatment
• Treatment with imatinib
  – Most appropriate for older patients at high risk from transplant-related mortality
  – Younger patients without a suitable donor
  – For patients in accelerated or blast phase.

Tyrosine kinase inhibitors

• Tyrosine kinase inhibitors slow or stop the actions of BCR-ABL
  – Leads to the rapid death of cells containing the Philadelphia chromosomes
  – Normal cells suffer less toxic effects from tyrosine kinase inhibitors as compared to traditional chemotherapy treatments

Imatinib (Gleevec)

• Can be used in patients with all phases of CML
• One study compared imatinib to interferon plus cytarabine for newly diagnosed, chronic phase CML
  – 97 percent of patients receiving imatinib had a complete hematological response rate
  – 76 percent achieved a complete cytogenetic response
  – Further follow-up is needed to determine how long responses will last
Gleevec

- Previously untreated patients in the chronic phase of CML
- CML in chronic phase after failure of treatment with interferon
- CML in accelerated phase
- CML in myeloid blast crisis
- Philadelphia chromosome positive acute lymphoblastic leukemia
- Pediatric CML

Monitoring Response to Imatinib

- Important to follow the disease status regularly, although the optimal method and interval remains uncertain
  - Quantitative PCR
  - FISH for bcr abl
  - Probably monitor peripheral blood every 3-4 months, ? How often to evaluate bone marrow

Side Effects

- Diarrhea
- Muscle cramps (treat with Mg or Ca)
- Skin rash
- Cytopenias
- Gynecomastia (from decrease in testosterone levels)
- Hepatotoxicity
- Cardiotoxicity/peripheral edema
Polycythemia

- Suspected when the HCT is >48% in women or >52 percent in men
- Suspected when the HGB is >16.5 in women or >18.5 g/dL in men

Polycythemia

- Relative polycythemia: isolated decrease in plasma volume can elevate the hemoglobin, hematocrit, and RBC count
- Absolute polycythemia: increased RCM
- Primary polycythemia: includes polycythemia vera and rare familial variants
- Secondary polycythemia: is most often due to an oxygen-sensitive Epo response to hypoxia, but can also result from the presence of an Epo-secreting tumor
- Combined polycythemia: increased RCM as well as a reduced plasma volume, a combination most commonly seen in smokers

Evaluation

- Once a high value for hemoglobin or hematocrit has been reported, it should be confirmed by repeat testing
- Obtain good history: most common cause of polycythemia is hypoxia secondary to pulmonary disease, medications and lifestyle activities, smoking history, chronic exposure to carbon monoxide
Physical examination

- Cyanosis: lips, fingers, earlobes
- Cardiac murmurs or bruits
- Hepatomegaly and splenomegaly
- Plethoric facies, dilated retinal veins, or areas of painful erythema may be seen in patients with polycythemia vera

Blood volume measurement:

- RBC mass (RCM) is directly determined following infusion of the patient's own RBCs labeled with a radioactive isotope, while the plasma volume is simultaneously and directly determined following infusion of isotopically-labeled human albumin
  - RBC mass: 24 to 30 mL/kg (normal)
  - Plasma volume: 39 to 49 mL/kg
  - "gold standard": but costly, time consuming
  - excellent correlation between RCM and HCT, the additional information obtained from blood volume studies may not be critical

Further evaluation

- If repeated CBC shows polycythemia
  - blood carboxyhemoglobin (COHGB) if exposure to tobacco smoke, engine exhaust, or other sources of carbon monoxide is a possibility
  - COHGB values in excess of 5 percent strongly suggest polycythemia secondary to CO poisoning
  - due to the presence of smoking-related polycythemia is prompt reversal of a low plasma volume following cessation of smoking (reduction in HCT of four or more percentage points within a few days of stopping smoking)
• If hypoxia is a possibility, screen with pulse oximetry
• A low oxygen saturation in the presence of normal arterial oxygen tension suggests the presence of high concentrations of carboxyhemoglobin or methemoglobin
• Serum erythropoietin: a low level with erythrocytosis is relatively specific for polycythemia vera

Secondary erythrocytosis

• Erythropoietin-producing neoplasms
  – Renal cell carcinoma
  – Hepatocellular carcinoma
  – Hemangioblastoma
  – Uterine fibroids
• Hypoxemia secondary to:
  – Chronic pulmonary disease
  – Right-to-left cardiac shunts
  – Sleep apnea
  – Massive obesity (Pickwickian syndrome)
  – High altitude
  – Red cell defects
    • Some cases of congenital methemoglobinemia
    • Chronic carbon monoxide poisoning (including heavy smoking)

Mgmt of secondary polycythemia

• Control of the underlying cause, if possible
• Limited phlebotomy, as tolerated, if symptoms are present
  – Such patients may achieve relief with reducing the hematocrit slightly, but may become more symptomatic if the hematocrit is reduced to the normal range
Polycythemia vera

- Occurs in all populations, and all age groups, including early adulthood and occasionally in children
- Incidence estimated to be 1.9/100,000 per year
- Highest incidence: men 70 to 79 years (24 cases/100,000 persons/year)

Prognosis

- Median survival of untreated PV is about 6 to 18 months from the time of diagnosis, survival of treated patients exceeds 10 years
- Main causes of death:
  - thrombosis (annual incidence of thrombosis 1.8 percent in patients below age 40; 5.1 percent in those over 70 years of age)
  - disease transformation into myelofibrosis with myeloid metaplasia (MMM) or AML (the rate of hematologic transformation is 1.3 episodes per 100 patients/year)

CLINICAL PRESENTATION

- Nonspecific complaints: fatigue, dizziness, sweating
- Pruritus, after warm bath: present in 43 percent
- Venous or arterial thrombosis (especially unusual ones: Budd-Chiari syndrome, portal, splenic, or mesenteric vein thrombosis)
- Gastrointestinal symptoms: PUD, heartburn
- Erythromelalgia (burning pain in feet/hands with erythema, pallor, or cyanosis, with palpable pulses) is common
  - platelet counts usually >400,000
PHYSICAL EXAMINATION

• Splenomegaly, facial ruddiness, and hepatomegaly most common
• Injection of the conjunctival small vessels and/or engorgement of the veins of the optic fundus
• Excoriation of the skin
• Stigmata of a prior arterial or venous thrombotic event
• Gouty arthritis and tophi

Laboratory findings

• Elevated hemoglobin/hematocrit
• Elevated red blood cell mass
• Platelet count >400,000/microL in 60 percent
• White blood cell count >12,000/microL in 40 percent
• Bone marrow cellularity increased
• Storage iron was absent from the marrow in 94 percent.

Diagnosis

• WHO criteria
  – Platelet count >400,000/microL
  – White blood cell count >12,000/microL
  – Low serum EPO levels
  – Bone marrow showing panmyelosis with prominent erythroid and megakaryocytic proliferation
  – Diagnosis: two of these criteria + elevated RCM, absence of secondary erythrocytosis (hypoxia, high affinity hgbS, malignancy)
Treatment

- Goals: to reduce symptoms and reduce thrombosis
- Phlebotomy to keep the hematocrit below 45 percent in men and 42 percent in women (helps reduce symptoms, not much benefit in reduction of thrombosis)
- Supplement phlebotomy with hydroxyurea in high risk for thrombosis (age over 70, prior thrombosis, platelet count >1,500,000, cardiovascular risk factors)

• If not contraindicated, aspirin at low dose of 75 to 100 mg (to reduce risk of thrombosis and ameliorate erythromelalgia)
• Anagrelide: in refractory thrombocytosis
• Allopurinol: if needed in hyperuricemia

Treatment of pruritus

- Reduce water temperature
- Starch baths
- Antihistamines
- Interferon alfa
- Danazol
- Paroxetine or fluoxetine (anecdotal)
Agnogenic myeloid metaplasia (AMM)/chronic idiopathic myelofibrosis (CIMF)

- Chronic myeloproliferation and atypical megakaryocytic hyperplasia leading to bone marrow fibrosis
- Hallmarks: marked splenomegaly, extramedullary hematopoiesis, severe constitutional/B symptoms with anemia and bone marrow fibrosis

- Least frequent among the chronic myeloproliferative diseases
- Estimated incidence of 1.5 per 100,000 per year
- Median age at presentation is 67 years

Clinical manifestations

- Signs and symptoms
  - Severe fatigue, weight loss, symptoms due to splenomegaly, fevers
  - Splenomegaly: hallmark of disease, usually massive
  - Hepatomegaly: portal hypertension/portal vein thrombosis common
  - Extramedullary hematopoiesis: spleen, liver, lung, lymph nodes, gi/gu tract, CNS, skin
  - Bone involvement: osteosclerosis, “superscan” on bone scan, severe bony pain
Diagnosis

- Bone marrow aspiration: classical "dry tap"
  - Bone marrow biopsy with fibrosis, atypical megakaryocytic hyperplasia and thickening and distortion of the bony trabeculae (osteosclerosis)
  - Absence of Philadelphia chromosome
  - Splenomegaly
Differential Diagnosis

- Malignancies metastatic to bone marrow
- Hairy cell leukemia, lymphoma, and multiple myeloma
- Other MPDs
- Autoimmune disorders (eg, systemic lupus erythematosus, scleroderma)
- Renal osteodystrophy or secondary hyperparathyroidism with vitamin D deficiency

Prognosis

- 3 year survival about 50%
  - However much worse survival with constitutional symptoms, cytogenetic abnormalities, anemia, advanced bone marrow fibrosis, leukocytosis/leukopenia, circulating blasts

Treatment

- SCT only potentially curable treatment
- Supportive treatment: transfusions, danazol, hydrea, splenic irradiation, thalidomide, prednisone, procrit
- Splenectomy can be considered for painfully enlarged spleen, anemia and other refractory cytopenias, and/or severe degrees of portal hypertension (high risk of mortality however)
Reactive thrombocytosis

- Much more common than a primary disorder
  - even with extreme thrombocytosis (platelet count >1,000,000/microL)
  - is a cytokine driven process
- Vasomotor (headache, visual symptoms, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia), thrombotic, or bleeding complications can occur, but more likely with a primary disorder
- Thrombo-hemorrhagic manifestations suggests the diagnosis of a primary disorder

Reactive thrombocytosis

- Acute blood loss, acute hemolytic anemia, iron deficiency anemia
- Metastatic cancer, lymphoma, reactive after myelosuppressive drug use
- Rheumatological disorders
- Tissue damage (trauma, burns, severe pancreatitis, post-splenectomy, post CABG)
- Chronic infections, tuberculosis
- Chronic renal disease
- After exercise
- Reaction to meds (vincristine, epinephrine, atra, interleukin 1-B)

Laboratory evaluation

- Ferritin to evaluate for iron deficiency
- Peripheral smear to evaluate for Howell-Jolly bodies (asplenia)
- Inflammatory or infectious conditions are likely to have neutrophilic leukocytosis (left shift)
- Serum C reactive protein, erythrocyte sedimentation rate, plasma fibrinogen (all increased with inflammatory/infectious process)
Essential thrombocytosis

- A clonal stem cell disorder
- Neither thrombopoietin or its receptor (c-Mpl) has been implicated
- Incidence rate is 2.5 new cases/100,000 population per year
- Life expectancy appears to be normal
- Female preponderance
- Median age at diagnosis is 60 years

Clinical manifestations

- 50% asymptomatic
- Thrombosis and hemorrhage are common
- Vasomotor symptoms
  - headache, lightheadedness, syncope, atypical chest pain, acral paresthesia, livedo reticularis, erythromelalgia, transient visual disturbances
Diagnosis

- Diagnosis is made by exclusion
- Fulfill all criteria
  - Consistent platelet count > 600,000
  - Megakaryocytic hyperplasia
  - Absence of the Philadelphia chromosome
  - Absence of causes for reactive thrombocytosis
  - Normal iron stores
  - Absence of MDS or myelofibrosis

Prognosis

- Most patients with ET enjoy a normal life expectancy
- Overall risk of thrombotic episodes in patients with ET: 6.6 percent/patient-year
- Risk of major bleeding episodes during the entire course is less than 5 percent and is probably not exacerbated by using low dose aspirin
Risk groups

- Low risk
  - Age <60 years
  - No previous history of thrombosis
  - Platelet count <1,500,000/microL
  - No cardiovascular risk factors (eg, smoking, obesity)

- Intermediate risk
  - Patients who do not qualify for either the low risk or high risk groups

- High risk
  - Age ≥ 60 years
  - A previous history of thrombosis

Treatment

- Most patients with ET have a normal life expectancy and are asymptomatic and can often be observed
- Vasomotor symptoms: low dose aspirin
- Hydroxyurea in high risk pts to lower platelet count
- Anagrelide if hydrea is not tolerated or does not control counts