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**Objectives**

1. Diagnose the four most common myeloproliferative disorders
2. Develop a framework and differential for erythrocytosis, leukocytosis, and thrombocytosis
3. Describe the basic principles of treating myeloproliferative disorders

**Teaching Instructions**

Plan to spend at least 30-60 minutes preparing for this talk by using the Interactive Board and clicking through the graphics animations to become familiar with the flow and content of the talk. All clickable elements are denoted by a rounded shaded rectangle and mouse cursor. There are questions that serve as prompts to engage the audience.

Begin with reviewing the objectives for the session. We recommend progressing in order, though this gives you the flexibility to deliver more focused teaching.The anticipated time it will take to give the talk is ~**30-45 minutes** to teach.

**Overview***Ask your learners “What is a MPN?” and click to reveal the answer.* Hematologic malignancies are differentiated into myeloid and lymphoid neoplasms. A subset of hematologic malignancies includes **myeloproliferative disorders** which are diseases of the hematopoietic stem cell leading to the overproduction of *mature* cells. This differs from a myelodysplastic syndrome where there is a disease of the hematopoietic stem cell leading to *abnormal maturation*.

The flow chart reviews normal hematopoiesis. *Click on “what are the most common MPNs” to reveal the answer.* Overproduction of thrombocytes (or platelets) leads to essential thrombocytosis (ET). Overproduction of erythrocytes leads to polycythemia vera (PV) (this is, however, an oversimplification as leukocytosis and thrombocytosis are commonly seen as well). Overproduction of mature granulocytes leads to chronic myeloid leukemia (CML). And finally, when the bone marrow is replaced by connective tissue, it can lead to primary myelofibrosis (PMF). These are the 4 most common MPNs. Each of the MPNs can transform into an aggressive form of bone marrow failure or acute leukemia. ET, PV, PMF are often grouped together because they are associated with 3 common driver mutations.

**Essential thrombocythemia**

*Click on “what is ET?” to reveal the answer.* ET is a disorder in which there is an increase in clonal production of platelets. It is associated with one of three driver mutations including JAK2, CALR, MPL. However, 10-20% of cases have no mutation that can be identified.

* *Signs/symptoms: Ask your learners what signs and symptoms are associated with ET and click on “Sign/symptoms?” to reveal the answer.* Clinically, ET may present with vasomotor symptoms, TIAs, ocular migraines, or 1st trimester pregnancy loss. Arterial or venous thromboses may occur but are less common. Some patients may be asymptomatic, and it is first discovered on a CBC. If the patient is negative for all three driver mutations (triple negative), a bone marrow biopsy may be necessary to confirm the diagnosis as thrombocytosis can be seen in others MPNs.
* *Differential Diagnosis:* The differential for thrombocytosis includes reactive versus primary thrombocytosis. Challenge learners to come up with examples of reactive thrombocytosis before clicking to reveal the answer. Reactive causes include iron deficiency anemia (commonly missed), in addition to infection/inflammation and post-splenectomy state. Primary causes include all 4 MPNs discussed in this talk.
* *Treatment:* The goal of treatment for ET is to prevent thrombosis. The magnitude of thrombocytosis does not increase the risk of thrombosis (or bleeding). Thrombocytosis alone without a diagnosis of ET does NOT warrant aspirin therapy. The treatment for ET depends on if the patient is low risk or high risk for thrombosis. If low risk, one can manage with active surveillance and low dose aspirin. If high risk, the patient will likely need aspirin therapy or anticoagulation depending on thrombosis history (venous vs arterial) and may need a cytoreductive agent (like hydroxyurea or pegylated interferon) as well.

**Polycythemia vera (PV)**

This is the most common type of all the MPNs. *Click on “what is PV” to reveal the answer.* Although a hallmark of PV is erythrocytosis, commonly leukocytosis and thrombocytosis are seen with PV as well. Over 95% of patients have the JAK2 V617F mutation.

* *Signs/ Symptoms*: Challenge your learners to come up with symptoms of PV before clicking to reveal the answer. Symptoms may include headaches, aquagenic pruritus, thrombosis, hemorrhage (from acquired von Willebrand’s disease), TIAs or ocular migraines. It should be suspected in males with Hgb >16.5, females with Hgb >16, a 25% rise in typical RBC mass, or if patient develops arterial or venous thrombosis. Maintain a high level of suspicion for PV in patients with a diagnosis of Budd-Chiari syndrome, portal vein thrombosis, splenic vein thrombosis, or mesenteric vein thrombosis as these conditions can result in portal hypertension which may mask the laboratory signs of PV.
* *Physiology of erythrocytosis:* To review other etiologies of erythrocytosis, it is important to understand the normal response to hypoxemia. In the setting of low oxygen in the blood (1), specialized cells in our kidneys (2) produce a hormone called erythropoietin (EPO) (3). This hormone stimulates our bone marrow (4) to produce more red blood cells (5) and thus can lead to an increase in the red blood cell mass.
* *Differential Diagnosis:* Causes of erythrocytosis can be separated into relative erythrocytosis, secondary erythrocytosis and PV. *Prompt learners to identify the primary problem in each type of erythrocytosis, give examples and determine what the measured EPO level would be. Click on each button until the mouse cursor disappears.*
  + *Relative erythrocytosis* is from hemoconcentration of the blood from dehydration (diuretics, vomiting, diarrhea). The graphic shows why measured hematocrit/ hemoglobin concentration would be higher in a patient who is dehydrated. EPO level in relative erythrocytosis is unchanged/normal.
  + *Secondary* erythrocytosis may be due to hypoxemia (COPD/OSA, high altitude, RAS) or elevated EPO levels (typically from EPO secreting tumor such as HCC, RCC, or pheochromocytoma). EPO levels in secondary erythrocytosis are elevated.
  + *PV* – in PV, the primary problem is at the level of the bone marrow. As a result, there is a negative feedback mechanism which suppresses EPO production. It is important to note that although EPO level is typically suppressed in PV, it may also be normal in as many as 15% of patients. EPO level is not the most sensitive or specific test; however, it may point you in the direction of the most likely diagnosis.
* *Treatment:* The basics of treatment for polycythemia vera are to prevent complications such as thrombosis. Patients are risk stratified into high or low risk depending on age and history of thrombosis. The mainstay of treatment includes phlebotomy and low dose aspirin. If high risk, you could consider adding a cytoreductive agent (such as hydroxyurea or pegylated interferon).

**Primary Myelofibrosis (PMF)**

*Ask learners what they recall about PMF before clicking on “What is PMF”.* This myeloproliferative disorder occurs when the bone marrow is replaced by connective tissue or fibrosis. It is associated with one of three driver mutations including JAK2, CALR, or MPL and can develop from other MPNs (PV or ET). When the bone marrow is replaced by fibrosis it can lead to extramedullary hematopoiesis.

* *Signs and symptoms* include hepatosplenomegaly, bone pain, anemia (from low red blood cells), bleeding (from low platelets), infections (from low white blood cells).
* Ask learners what they would expect to see on a peripheral smear or a bone marrow biopsy in a patient with myelofibrosis. *Click on each of these to reveal the answer.* Teardrop cells (dacrocytes) and a “dry tap” are classic findings.
* *Treatment:* The only known curative treatment option for PMF is hematopoietic stem cell transplant. This is reserved for patients with poor prognostic features who are good transplant candidates. Online tools exist to help predict outcomes and prognosis after HSCT (Here is an online example: <http://www.mipss70score.it/>).
  + Overall, If the patient has a good prognosis, they may be monitored with active surveillance and symptom control for cytopenias with transfusions. EPO stimulating agents can be considered for patients with transfusion dependent anemia.
  + If the patient is transplant ineligible with poor prognosis, you can consider Janus Kinase inhibitors (such as ruxolitinib) or hydroxyurea.

**Chronic myeloid leukemia**

*Ask your learners to come up with what they know about CML before clicking on “What is CML” to reveal the answer.* CML is a malignancy associated with an increase in mature granulocytes (neutrophils, basophils, eosinophils). CML is associated with BCR-ABL fusion gene also known as the Philadelphia Chromosome. This mutation leads to an increase in tyrosine kinase activity. Although granulocytes in CML are morphologically normal, they are cytochemically abnormal and have a low leukocyte alkaline phosphatase (LAP) score.

* *Differential of leukocytosis:* Typically, the work up for CML begins when leukocytosis is discovered on a complete blood count. Challenge learners to come up with a differential for leukocytosis including a leukemoid reaction (infections, stress, medications, tobacco use, etc) vs malignant etiologies. A history that may be more suspicious for CML include constitutional symptoms (weight loss, fever, fatigue), abdominal fullness. Labs that are suspicious for CML include neutrophilia with a left shift, basophilia, or eosinophilia without a clinical suspicion for a leukemoid reaction. Although the WBC can be high in CML (>100,000), leukostasis is much rarer compared to similar WBC levels seen in acute leukemia.
* *Natural disease course of CML:* That natural disease course of CML without treatmentincludes a chronic phase, an accelerated phase, and a blast crisis (which can resemble acute leukemia). However, with treatment, many patients can have normal life expectancies. Most patients are diagnosed in the chronic phase (85% of patients) and can be asymptomatic when diagnosed.
* *Treatment:* The treatment for CML is typically a tyrosine kinase inhibitor (TKI). Imatinib was the first TKI approved for CML and revolutionized treatment for what was previously thought of as a fatal disease. There are now multiple approved next generation TKIs. If patients develop resistance to a TKI (seen on BCR/ABL1 testing), they may be switched to another TKI. Allogeneic stem cell transplantation is now very rare and only considered if the patient fails later lines of therapy. The blast phase of CML may require induction chemotherapy (like acute leukemia) in addition to TKI. Patients can be monitored for BCR/ABL levels using the peripheral blood in order to track responses to treatment and need for resistance mutation testing.
* *Leukemias* - Click on the "Leukemias" button in the left hand table of contents to learn more about different types of leukemia. Click on each type of leukemia until the cursor disappears to learn more about demographic, diagnosis, and complications. If the patient history and labs are concerning for malignant etiologies, it will be important to further differentiate the four main types of leukemias – AML, CML, ALL, CLL. The following table helps to show the main findings on peripheral smear and bone marrow biopsy that you would expect to see in the four broad categories of leukemias. It is important to highlight the classic smear findings in addition to number of blasts in the bone marrow, demographics, and other unique features. Of note, acute leukemias may develop leukostasis or hyperleukocytosis, which are hematologic emergencies, but these complications are much less likely with CML and CLL (which often can tolerate higher WBC levels).

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|  | **AML** | **CML** | **ALL** | **CLL** |
| Peripheral smear | Myeloblasts  Auer rods | Eosinophilia/ basophilia  Median WBC 100k | Lymphoblasts | Lymphocytosis  Smudge cells |
| Bone marrow | >20% myeloblasts | Granulocytic hyperplasia  Typically <20% myeloblasts | >20% lymphoblasts | Lymphocytic hyperplasia |
| Demographic | Adults > children | Median age 50 |  |  |
| Unique features | DIC (especially in APML) | T(9;22) BCR-ABL1 fusion | * Can infiltrate lymph nodes * CNS infiltration (needs LP prior to treatment) | * Can infiltrate lymph nodes * Richter transformation (high grade lymphoma) * Autoimmune cytopenias |

**Take Home Points**

1. There are four main types of myeloproliferative disorders: polycythemia vera, essential thrombocythemia, chronic myeloid leukemia, and primary myelofibrosis
2. An erythropoietin level can be useful in distinguishing secondary polycythemia from polycythemia vera
3. Treatment of myeloproliferative disorders typically depends on risk stratification (PCV/ET) and prognosis (MF). CML treatment is highly effective.

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