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**Objectives:**

1. Identify the progression of normal bone marrow differentiation and points of pathologic mutation in AML
2. Diagnose AML using common clinical and laboratory findings
3. Diagnose and manage common complications of AML

Bonus Objectives: Risk Stratification, Management

**Teaching instructions:** Plan to spend at least 30-60 min preparing for this talk by reviewing the teaching script and clicking through the graphic animations on the Interactive Board to become familiar with the flow and content of the talk. Print out copies of the Learner’s Handout so learners may take notes as you expand on the management and apply it through practice cases.

**The anticipated time to deliver this talk is about 20-30 minutes.**

Begin with reviewing the objectives for the session. The epidemiology of AML is optional but can be helpful review and understand as the teacher. We recommend progressing through the talk in order. However, you may adapt the talk and content to any allotted time (e.g., reviewing complications of AML only). All clickable buttons/elements are indicated by a cursor icon. Each button can act as a prompt for you to engage your learners.

**Epidemiology/ Background (*Epidemiology*)1**

*This section is optional and will take ~5 min to review. Ask your learners each of the prompt questions. Click on each button to reveal the answers.*

* **How common is AML?** – AML accounts for about 1% of new cancers or ~20k new diagnoses annually. This is significantly lower than incidence rate of other cancer such as lung (~230k annually), breast (~270k annually), and colon cancer (~150k annually)*.*
* **What is the prognosis?** –Overall, prognosis is very poor. Without treatment, survival is extremely limited – on the order of days to weeks. With treatment, only **1 in 3** will survive to 5 years after diagnosis.
* **Who gets AML?** – This disease predominantly affects the **elderly**, with the median age of diagnosis being 68 years old. However, AML can affect people of any age.

**Objective 1: Identify the progression of normal bone marrow differentiation and points of pathologic mutation in AML (*Pathology – Normal, AML)***

*Click on “Normal” and “AML” on the left upper-hand navigation bar to review normal bone marrow differentiation and pathologies in AML.*

* **Normal bone marrow physiology** – Review normal bone marrow physiology. A simplified diagram is shown here. Hematopoietic stem cells in the bone marrow differentiate into lymphoid and myeloid stem cells. Lymphoid stem cells then differentiate into lymphoblasts, which subsequently differentiate into T, B, and NK cells. Myeloid stem cells differentiate into myeloblasts which subsequently become leukocytes. Myeloid stem cells also become RBCs and platelets.
* **Where is the pathology of AML?** –*Ask your learners where the pathology is in AML and click to reveal the answer.* Mutations in myeloid stem cells and myeloblasts are largely responsible for the development of AML via *over-proliferation*. *Click on “AML” in the navigation bar.* Given the disease affects precursors to RBCs, WBCs, and platelets, predictably these cell lines are often abnormal. *Ask learners for each given CBC where they think the mutation might be and how it is causing abnormalities.*
  + *Isolated leukocytosis -* If the pathology is affecting the myeloblast, the WBCs will be the predominant cell line affected. Depending on the specific mutation, this can lead to very low or very high levels of WBCs.
  + *Leukocytosis + cytopenias -* However, even if only the myeloblast is affected, the other cell lines may still become disrupted through various mechanisms such as variations in cytokines such as IL-6. While the percentage of blasts does not necessarily correlate to peripheral cytopenias, aberrant replication can become so severe that it crowds out other developing cells in the bone marrow leading to more cytopenias.
  + *Pancytopenia* - In the case the myeloid stem cell is solely affect, you are more likely to see proportionate declines across all cell lines leading to pancytopenia.

**Objective 2: Diagnose AML using clinical and laboratory findings (*Diagnosis*)**

* **Diagnostic criteria** – In general, there are two key components to the diagnosis of AML, both of which must be present to make the diagnosis.
  + ≥20% blasts, either in the bone marrow (bone marrow biopsy) or peripheral blood (peripheral smear). While this is a general rule, there are several nuanced exceptions.
  + Cells must be of myeloid origin. This is determined by either presence of Auer rods, MPO (+), or sufficient myeloid markers on immunophenotyping.
  + Presence of cytogenetic abnormalities such as t(6;9) or Core-Binding Factor (CBF) that, if present, are diagnostic of AML regardless of blast count.
* **Clinical and laboratory findings –** The diagnosis of AML often requires uncommonly ordered tests. However, some clinical and laboratory abnormalities should raise suspicion and prompt further evaluation for AML... *Click on each of the components to reveal additional information.*
  + *WBC* – AML can present with both leukocytosis or leukopenia as previously discussed. The median WBC count is 15k. Hyperleukocytosis with WBC >100k is seen in ~ 10-20% of patients on presentation2,3. Leukopenia is seen in ~25% of patients. The peripheral smear may show blasts, which should prompt further evaluation. The presence of **Auer Rods** is diagnostic of AML if present.
    - Physical exam findings associated with WBC abnormalities in AML include gingival hyperplasia (from leukemic infiltration of gingival tissue) and leukemia cutis (from leukemic infiltration of the skin). Sweet syndrome (acute febrile neutrophilic dermatosis) is an even rarer dermatologic finding that can be associated with AML and other malignancies.
  + *Hgb* – Anemia is commonly seen and may result in conjunctival or palmar pallor. Anemia in conjunction with thrombocytopenia should also raise suspicion for complications of AML such as DIC.
  + *Platelets –* Thrombocytopenia is seen in almost all patients with ~25% of patients presenting with plt count <25k. Thrombocytopenia may result in petechia or purpura.

**Objective 3: Diagnose and manage emergent and life-threatening complications of AML *(Complications)***

While AML will be a rare diagnosis for them to make, it is essential to have it in mind as these patients will likely see a general team prior to a specialist, and given the severity of complications, early recognition is essential.

Click on each of the following clinical scenarios to reveal the corresponding complication. Challenge learners to identify signs/symptoms, diagnostic criteria, and basic initial management steps. Click on each section to reveal the answer.

* **Leukostasis** – Hyperleukocytosis (elevated WBC) and associated cytokine production lead to increased blood viscosity which results in impaired tissue perfusion.
  + Symptoms: This most commonly presents as neurologic (focal neurologic symptoms, headache, altered mentation) with respiratory changes (hypoxia, diffuse alveolar or interstitial infiltrates) being another prominent manifestation.
  + Diagnosis: Made clinically by the presence of hyperleukocytosis (typically WBC >100k, though can occur with WBC counts as low as 50k).
  + Treatment: Overall, treatment is focused on reducing the number of WBCs. *A bonus point that may be highlighted is that leukapheresis is* ***contraindicated*** *in APL specifically as it can exacerbate coagulopathy.*
* **Tumor Lysis Syndrome (TLS)** – TLS is an oncologic emergency that is caused by massive cell lysis with release of intracellular electrolytes and nucleic acids.
  + Symptoms: May include lethargy, anorexia, seizures, syncope, but are generally nonspecific and vague.
  + Diagnosis: Laboratory findings are diagnostic. As cells break down and release their intracellular contents, resulting in hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. These patients may additionally develop resultant AKIs (from crystal nephropathy) and fatal cardiac arrythmias.
  + Treatment: Prevention and initial treatment include allopurinol and IVFs, with more severe cases warranting rasburicase.
* **Disseminated Intravascular Coagulation** **(DIC)** –The coagulation cascade is aberrantly over-activated resulting in consumption of coagulation factors. These patients are both coagulopathic and thrombogenic.
  + Symptoms: Signs of bleeding (bruises, nosebleeds, gum bleeding) should raise concern, with classic description of “oozing from IV site.”
  + Diagnosis: Coagulation panel will be abnormal with elevated PT, PTT, INR and D-dimer. Low fibrinogen is crucial to diagnosis (and management).
  + Treatment: Supportive transfusions help as temporizing measures, but definitive management requires treatment of the malignancy.
* **Febrile Neutropenia** –. It is important to evaluate neutropenic patients for *any possible signs of infection*. While there are different severities of neutropenia, the most important number is **ANC <500** (severe neutropenia). This includes patients who are expected to have an ANC <500 over the next 48 hours (such as those who recently received chemotherapy). There is additional risk for bacterial infection in *profound neutropenia (ANC <100)*. Pseudomonas coverage (cefepime or piperacillin-tazobactam) is always indicated and can be used as monotherapy. MRSA coverage is not empirically indicated, however should be added for at-risk patients including catheter-related infections, SSTI, PNA, or if patient is floridly septic or unstable. *Bonus point: it is frequently recommended to avoid Tylenol use among hospitalized neutropenic patients so as not to mask fever which may be the only sign of impending sepsis.*

**Bonus Objectives (Management - Risk Stratification, Treatment)**

A hematology service will likely be ordering these additional tests. However, generalists are often involved in their care, and it may be helpful to understand the basics of stratification, treatment, and prognosis.

Risk Stratification

There are several different ways of classifying AML based on things such as morphological cell type (FAB), cytogenetics (SWOG) and molecular markers (ELN)4. ELN will be used as an example and helps to predict prognosis by sorting patients based on cytogenetics and Next Generation Sequencing (NGS). Cytogenetics evaluates for large chromosomal changes (translocations, deletions, etc.), while NGS runs a gene panel assessing for *single gene mutations* known to be associated with AML. This not only aids in prognosis but can guide treatment with targeted therapies.

This most important takeaway for the non-hematologist is how significant the difference in prognosis is: 46% 5-yr OS with favorable risk vs. 4% 5-yr OS with adverse risk.

Approach to Therapy

Compared to solid organ malignancies which incorporate surgery and radiation and therefore use the framework of adjuvant/neoadjuvant – hematologic malignancies are only treated with systemic therapies.

* **Induction** – This is the first line treatment used and can be thought off as *treating the cancer that is detectable*. The goal with induction therapy is to knock down the cancer cells to a point they can no longer be detected. The most common induction therapy which has been the mainstay for 40+ years is “**7+3 regimen.**” *Emphasize the potency of this regimen, as it consists of 7 continuous days of cytarabine coupled with anthracycline infusions on each of the first 3 days*. *Hence, 7+3. This is an intense regimen not all patients can tolerate.* For those patients unable to tolerate this intense regimen (such as elderly patients or patients with poor functional status, most will instead receive Venetoclax/Hypomethylating Agent (HMA) as it is better tolerated).
* **Consolidation** – If induction is successful and after treatment the cancer cells are no longer detectable, frequently patient will undergo additional treatment called consolidation to *treat cancer that is presumably still present in low levels, despite being undetectable*. For AML, one of the most common forms of consolidation therapy is allogeneic stem cell transplant, as it offers the possibility of true cure.
* **Relapsed Disease or Disease Refractory to treatment** – Unfortunately, most patients will fall into this category at some point. Relapsed disease refers to patients with an initial response to treatment, then later have disease progression. Refractory disease refers to patients who did not have a response to initial treatment. Depending on a variety of factors (prognosis, age, overall fitness), patients will often be periodically faced with the choice of pursuing additional salvage/targeted therapy vs. transitioning to comfort-focused care.
* **Maintenance** – Maintenance therapy can be employed in a few different scenarios and is sometimes a risk/benefit discussion between patient and provider; the principle is to keep patients on suppressive treatment to delay or prevent relapse of disease.

**Take Home Points:**

1. A diagnosis of AML, while a relatively rare cancer, carries high associated morbidityand mortality.
2. AML arises from aberrant proliferation of myeloid precursor cells which can disrupt production of other cells lines (RBCs/ platelets).
3. Detection of AML is typically via laboratory analysis of peripheral blood smear, bone marrow biopsy, or cytogenetic abnormalities.
4. Life threatening AML complications include leukostasis, DIC, tumor lysis syndrome, and neutropenic fever.

**Cases**

**Case 1:** Patient presenting with pancytopenia and fevers and found to have Neutropenic Fever. Favorable prognosis, relatively young, therefore would likely treat with 7+3.

**Case 2:** Patient presenting with signs of bleeding, found to be pancytopenic. Smear shows Auer rods, which is diagnostic of AML, and schistocytes which should prompt concern for DIC. Found to be APL which has distinct treatment (ATRA/Arsenic). Long-term prognosis is excellent – the deadliest time for patients with APL is during the acute phase.

**Case 3:** Patient with weight loss and neuro changes. Found to have high WBC c/f Leukostasis. Labs show signs of TLS. Management likely via leukapheresis (given significant symptoms) and allopurinol + IVFs for TLS. Given age >75 unlikely to do well with 7+3, would likely receive Ven/Aza.

**References:**

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