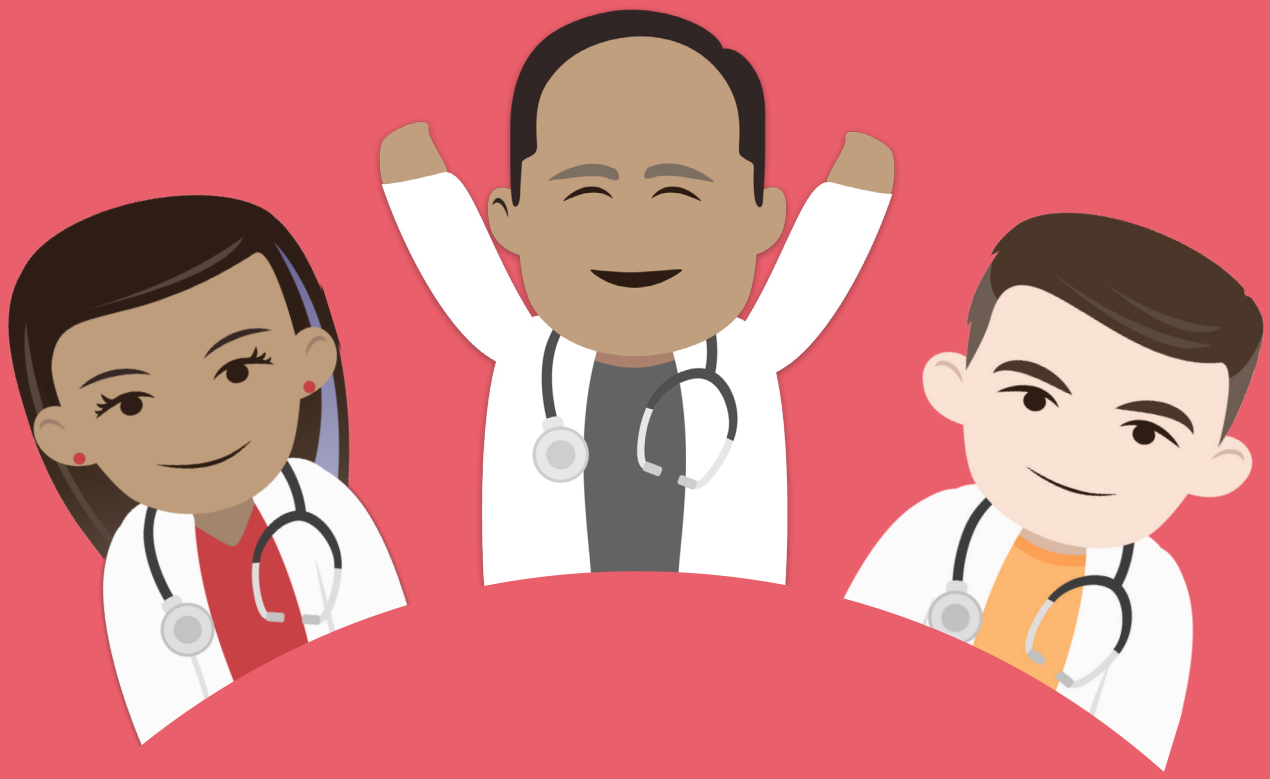
Hematology and Coagulation Essentials
Chapter 5

DIFFERENTIATING COMMON HEMATOLOGIC MALIGNANCIES



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Differentiating common hematologic malignancies

DIAGNOSING ACUTE LEUKEMIAS

Acute leukemia is suspected when a patient presents with leukocytosis along with anemia and thrombocytopenia. The leukemic cells give rise to a high white cell count and the production of red cells and platelets are suppressed in the bone marrow, producing the characteristic anemia and thrombocytopenia. Although not impossible, it is quite rare for a patient to present with acute leukemia without some degree of anemia and thrombocytopenia. Sometimes the white cell count is also suppressed and this gives rise to pancytopenia.

A peripheral blood smear should be ordered, looking for blasts. Blasts are highly abnormal cells that are not seen in normal blood. Acute leukemia is one of the few cases where blasts may be seen in the peripheral blood. In fact, if blasts are seen then acute leukemia is probable.

Acute myeloid leukemia (AML)

AML blasts typically make up > 20% of cells in the bone marrow. In AML, the blasts are granulocyte precursor cells known as myeloblasts. It is sometimes possible to identify myeloblasts by their morphology. However, confirmation requires flow cytometry, which can detect myeloblasts based on their antigenic profile.

A bone marrow study to assess WBC morphology is indicated for any patient with acute leukemia. Flow cytometry, cytogenetic studies, flourescence in situ hybridization (FISH), and polymerase chain reaction (PCR) can also be performed on the bone marrow samples.

Cytogenetic studies can be used to identify certain chromosomal abnormalities which are conclusive for AML, including

- t(15;17)
- t(8;21)
- t(16;16)
- Inv 16

The presence of any of these abnormalities is conclusive for AML, while t(15;17) is commonly associated with acute promyelocytic leukemia (APL).

PCR studies can be used to test for the presence of

- PML-RARA (associated with APL)
- FLT3
- NPM1
- CEBPA

Identification of the latter three genes can assist with predicting the prognosis for AML patients. For example, individuals with FLT3 generally do poorly.

Acute lymphoblastic leukemia (ALL)

In contrast to acute myeloid leukemia (AML), ALL presents more often in children than adults.

In ALL, the blasts are lymphocyte precursor cells known as lymphoblasts. It is sometimes possible to identify lymphoblasts by their morphology; however, confirmation requires flow cytometry, which can detect lymphoblasts based on their antigenic profile.

A bone marrow study to assess the morphology of WBCs is indicated for any patient with acute leukemia. Flow cytometry, cytogenetic studies, flourescence in situ hybridization (FISH) and polymerase chain reaction (PCR) can also be performed on the bone marrow samples.

In contrast to AML, there are no specific cytogenetic abnormalities which are conclusive for ALL. Cytogenetic studies are still performed, however, since the presence of certain chromosomal abnormalities may affect prognosis.

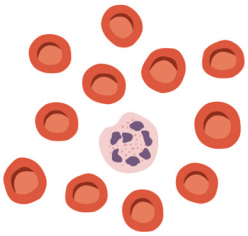
Unlike AML, PCR studies are not as useful in ALL. An exception is Philadelphia chromosome positive ALL, which generally has a poor prognosis. The molecular abnormality associated with the Philadelphia chromosome is a BCR-ABL transcript, which may also be detected by PCR.

While they all represent acute leukemias, ALL, AML, and acute promyelocytic leukemia (APL) are treated differently. Therefore, it is essential to arrive at an early diagnosis, so that effective treatment can be started early.

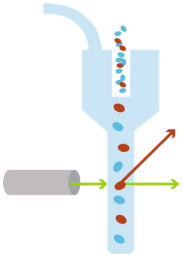
The steps for diagnosing and distinguishing between ALL, AML, and APL involve

1. Peripheral smear examination, and if necessary, flow cytometry on peripheral blood.

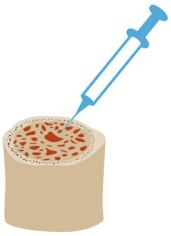
2. Bone marrow study with assessment of morphology, flow cytometry, cytogenetics, and molecular studies.



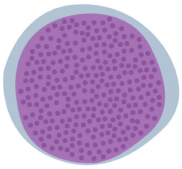
Peripheral smear



Flow cytometry



Bone marrow study



Morphology

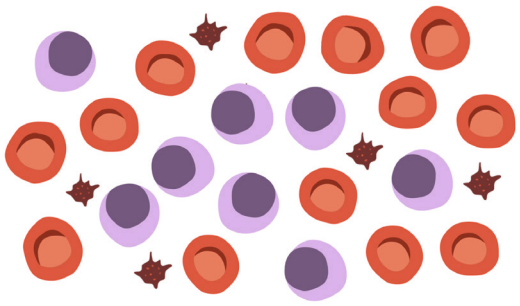
Cytogenetic

Disseminated intravascular coagulation (DIC) presents a mortal danger to APL patients if treatment is not started quickly. Thus, it is important to make a diagnosis of APL quickly.

Differentiating common hematologic malignancies

CONFIRMING CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Chronic lymphocytic leukemia (CLL) is an example of chronic leukemia. It is typically characterized by a high WBC count with lymphocytosis. The absolute lymphocyte count should be greater than 5,000 and be persistent.



CLL has different stages. Depending on the stage of CLL there may be thrombocytopenia or anemia; however, neither is seen in the earlier stages of CLL.

In contrast to acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), blasts are not seen in CLL.

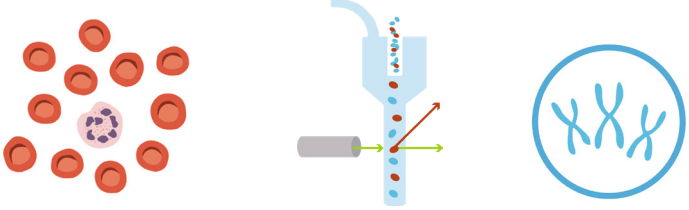
Unlike other leukemias, a bone marrow study is not essential for CLL. If a bone marrow study is performed, we can order flow cytometry, cytogenetic, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR) studies.

Flow cytometry performed from the peripheral blood is usually sufficient to diagnose CLL.

In CLL, flow cytometry demonstrates the presence of a population of B lymphocytes, which express certain antigens (CD5 and CD23) that are not normally expressed by B cells. Normal B lymphocytes carry immunoglobulins, consisting of kappa or lambda light chains, on their surface. A normal population of B lymphocytes will have some B cells containing kappa and some containing lambda light chains. In CLL, the B cells are abnormal. This abnormal population all have either kappa or lambda.

No specific cytogenetic abnormalities are diagnostic for CLL. There are, however, certain cytogenetic abnormalities which impart poor prognosis and others which impart good prognosis.

PCR studies are typically not required for CLL.



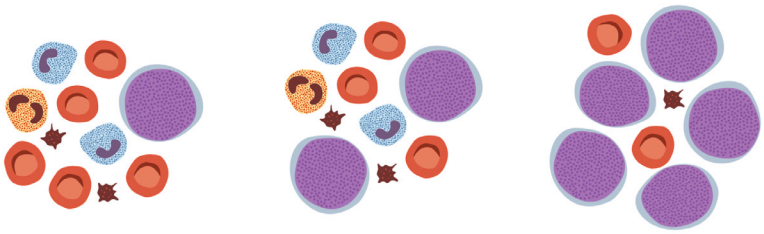
Peripheral smear | Flow cytometry | Cytogenetic

Differentiating common hematologic malignancies

IDENTIFYING CHRONIC MYELOGENOUS LEUKEMIA (CML)

Chronic myelogenous leukemia (CML) is a type of chronic leukemia.

There are three stages of CML: chronic, accelerated, and blast crisis phase.



Chronic phase | Accelerated phase | Blast crisis phase

Most cases of CML are diagnosed in the **chronic phase**. In the chronic phase, the WBC count is generally high, but few blasts are present in the circulation. The number of basophils and eosinophils are typically high; basophilia is almost always seen in CML.

Blasts may be seen in CML. In the chronic phase, blasts represent < 10% of WBCs. In the accelerated phase, 10–20% of WBCs may be blasts, and in the blast crisis phase, this number typically exceeds 20%.

Diagnosis of the **accelerated phase** is based on other diagnostic criteria. These are best left to the pathologists.

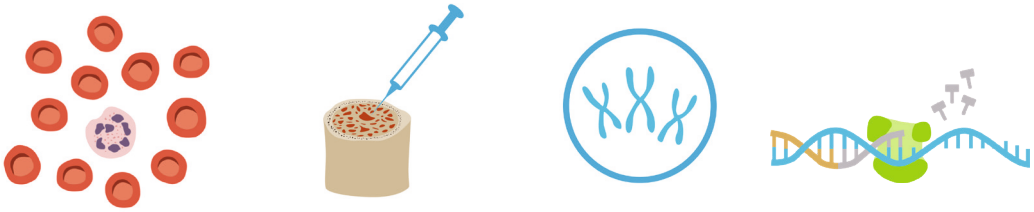
A bone marrow study is indicated for any patient with CML. The morphology of WBCs can be assessed from a bone marrow study.

Unlike other leukemias, flow cytometry is not useful for CML, because the neoplastic cells do not express any abnormal antigens.

Cytogenetic study, flourescence in situ hybridization (FISH), and polymerase chain reaction (PCR) studies should be performed on the bone marrow samples.

Cytogenetic studies from peripheral blood or bone marrow are very useful in CML. Patients with CML possess the Philadelphia chromosome, which is denoted as t(9;22).

In CML, PCR should be used to test blood or bone marrow for the presence of the BCR-ABL transcript. The Philadelphia chromosome or the BCR-ABL transcript must be present in order for a patient to be diagnosed with CML.

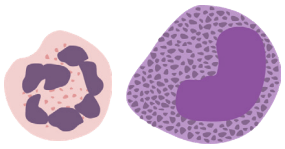


Peripheral smear | Bone marrow study | Cytogenetic | PCR

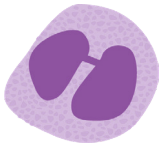
Differentiating common hematologic malignancies

DETECTING MYELODYSPLASTIC SYNDROME

In myelodysplastic syndrome (MDS) the bone marrow produces poor quality cells, which results in morphological changes. We call these abnormal cells dysplastic. The bone marrow attempts to destroy these abnormal cells, rather than send them out into the circulation. Thus, the bone marrow is hypercellular and the peripheral blood has low cell counts, resulting in unicytopenia, bicytopenia, or pancytopenia. This condition is usually seen in older adults.



Dysplastic cells



Pseudo Pelget-Huet cell

Dysplastic RBC

A peripheral smear should be ordered to look for these dysplastic cells.

Blasts may be present in the peripheral blood or their numbers may be increased in the bone marrow. Blasts usually make up < 20% of cells. If the percentage of blasts was > 20%, then the patient would have acute myeloid leukemia (AML).

A bone marrow study is always indicated for MDS to screen for the presence of abnormal dysplastic cells.

In MDS, flow cytometry can be used to quantify the percentage of blasts in the peripheral blood or bone marrow.

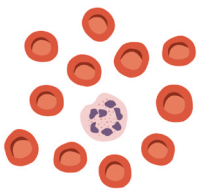
Polymerase chain reaction (PCR) studies are typically not ordered for MDS.

Fluoresence in situ hybridization (FISH) studies are of value in MDS, and studies can be perfomed on peripheral blood or bone marrow.

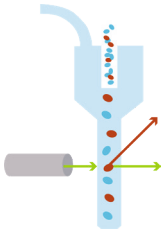
To establish a diagnosis of MDS, the following tests should be ordered:

- CBC and peripheral smear
- Flow cytometry (mainly to assess blast percentage)
- Cytogenetics and FISH studies of bone marrow

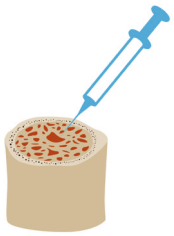
CBC



Peripheral smear



Flow cytometry



Bone marrow study

Cytogenetic

FISH

RECOGNIZING MONOCLONAL GAMMOPATHIES

Monoclonal gammopathy is a disorder in which there is the presence of an abnormal protein, called a paraprotein, in the blood. These abnormal proteins are immunoglobulins produced by neoplastic populations of B lymphocytes or plasma cells. Thus, monoclonal gammopathies occur in patients with B cell lymphoma or plasma cell dyscrasia.

Serum protein electrophoresis can be used to detect monoclonal gammopathy. This test can be performed on gels or by capillary method.

If the serum electrophoresis is positive, then we need to confirm the presence of paraprotein and determine the isotype by immunofixation.

Immunofixation can be performed on serum or urine. Urine immunofixation is used to determine whether the protein has passed into the urine. If paraprotein is present in the urine, it may indicate kidney damage and the patient will develop, or already has developed, leakage of protein in the urine (proteinuria).

If a plasma cell neoplasm is suspected, a bone marrow examination should be ordered to determine whether the bone marrow contains a neoplastic population of plasma cells. By definition, a neoplastic population of plasma cells will demonstrate light chain restriction. Normal plasma cells produce immunoglobulins containing either kappa or lambda light chains.

A normal population of plasma cells will produce immunoglobulins with a mixture of kappa and lambda light chains. A neoplastic population of plasma cells will produce immunoglobulins containing only kappa or lambda light chains.

Flow cytometry is able to identify the types of light chains present in the cytoplasm of plasma cells. Thus, flow cytometry can be used to identify a neoplastic population of plasma cells.

Cytogenetic studies are also commonly carried out for monoclonal gammopathy. While these studies do not have diagnostic value, they do show prognostic value.

Fluorescence in situ hybridization (FISH) studies are of value in monoclonal gammopathy. Like cytogenetics, they are of prognostic value.

Polymerase chain reaction (PCR) studies are typically not useful in monoclonal gammopathy.

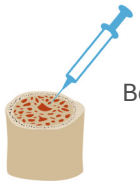
A patient with monoclonal gammopathy, due to a plasma cell neoplasm, may have

- Monoclonal gammopathy of undetermined significance (MGUS)
- Smoldering myeloma (SMM)
- Multiple myeloma (MM)
- Plasmacytoma / solitary myeloma

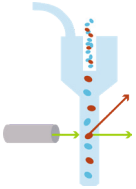
There are clinical criteria for each.

To establish a diagnosis of monoclonal gammopathy, the following tests should be ordered

- Bone marrow examination
- Flow cytometry



Bone marrow study



Flow cytometry