Hematologic malignancies

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Hematologic malignancies include a large number of seemingly similar but biologically diverse disorders. They include the spectrum of MDS/leukemias and lymphomas. Leukemias are the most common childhood malignancies and the most common of which is ALL. CLL is extremely rare in childhood and won't be covered here. Before detailing specific disorders, it's very helpful to clarify a few concepts:

1) Blood cell lines: there are 2 cell lines, not three. Red blood cells and platelets belong to the same cell line which is the myeloid cell line. Lymphocytes form the other cell line, the lymphoid. The rest of white blood cells belong to the myeloid cell line. So, next time when you look at a CBC, don't think of red blood cells, white blood cells and platelets as three distinct cell lines. This is extremely important since some disorders affect only the lymphoid line such as lymphomas while other affect only the myeloid line such as aplastic anemia.
2) Classifying tumors into malignant and benign isn't a very straight forward task. While for many tumors it may be clear to which category they belong, for many others, its not. For example, some benign tumors, such as meningioma, have the potential to metastasize, and for some malignant conditions, such as chronic phase CML, the tumor does not show clonal evolution.
3) Both lymphoblastic leukemias and lymphomas originate from lymphocytes. The main differentiating factor is that leukemias affect the bone marrow space, although they can infiltrate soft tissues (extramedullary leukemias) while lymphomas develop peripherally but they can still involve the bone marrow. The reason these entities affect different anatomic places although they originate from the same cell type is that they occur at different stages of evolution of the lymphocyte, are caused by different mutations and the cancer cells have different phenotypes thus they behave differently. If a lymphoma involves the bone marrow space and more than 20% of the marrow carries the malignant phenotype, this entity becomes a lymphoblastic lymphoma and is treated like a leukemia.

Following, is an account of the most common hematologic malignancies with the main clinical features of each. Rare entities won't be discussed here.

A) Leukemias:

1) Myelodysplastic syndrome (MDS)

While MDS is not a leukemia on its own, its natural history is to invariably evolve into one although the time to progress from MDS to AML is very variable. Most pediatric AML develops de-novo without a preceding MDS, unlike in older patient populations. Most adult MDS is primary, while pediatric MDS is usually either secondary to prior therapy or associated with a genetic syndrome. MDS is a myeloid cell line disorder in which the cells have abnormal structure (dysplasia) and function. It may or may not be associated with increased bone marrow blast population. An abnormal clone does evolve in this process, but it's not considered a leukemic clone until it usually counts for 20% of the bone marrow white blood cell population. This dysplastic change leads to cytopenia in 1 or more of the myeloid cell types (RBC, PLT, neutrophils). Median age at presentation is about 7 years but can virtually happen at any age. MDS is also characterized many times by certain cytogenetic abnormalities such as monosomy 7 or 5q deletion. The only curative treatment for MDS is stem cell transplantation.

2) Acute myeloid leukemia, AML: MDS and AML can be thought of as a continuous spectrum where most patients with MDS eventually progress to acute although the time to progression is very variable and can be anywhere from weeks to many years. Still. AML incidence at birth is very low, about a few cases per million a year. Incidence increased throughout life to over 150-175 cases per million a year. Monozygotic twin studies show the younger the patient, the more likely congenital (but not necessarily hereditary) factors play a factor in AML formation. If

the first twin develops AML in the first year of life, then concordance rate is very close to 100% with only a few weeks of latency until the second case. Concordance drops to about 20% in the index case is diagnosed between 1-6 years of age and drops significantly after the age of 6. Indeed, different mutations are associated with AML developing in these three time frames. It usually presents with fatigue, pallor, fevers, bone pain and occasionally bleeding due to thrombocytopenia. Many disorders can predispose to AML, including Fanconi anemia, dyskeratosis congentia, Diamond-Blackfan anemia, Schwachman- Diamond syndrome, severe congenital neutropenia and congenital Amegakaryocytic thrombocytopenia. Details about these are provided in other sections. The commonly used classification until recently used to be the FAB (French, American, British) system which depends on morphology. Where leukemias are classified according to phenotype and differentiation into 8 categories from M0-M7. This classification required the presence of 30% blast population in the bone marrow and anything under that is considered MDS. The shortcoming of this system is that since it depends mainly on morphology, it did not reflect prognosis or guide treatment. Now, we use the WHO system that requires only 20% blasts in the bone marrow this including more patients under the AML umbrella (this is significant since MDS is mainly treated with observation or stem cell transplant if it evolves into leukemia). The main features of this system are:

A) If leukemia is secondary due to radiation or chemotherapy, its classified as therapy related or secondary AML which has a poor prognosis.
B) If the leukemia is in a patient with Down syndrome then its down syndrome related AML which generally has an excellent prognosis.
C) If the bone marrow shows one of the 4 AML defining genetic abnormalities, namely, t (8;21), inv (16), t (15;17) or MLL rearrangement then it's called AML with (the specific genetic abnormality). If one of these abnormalities is demonstrated, then we don't need the 20% blast condition to diagnose the leukemia. Among these abnormalities, MLL-r is associated with poor prognosis while the others have a good to excellent prognosis.
D) If the marrow shows signs of dysplasia or one of the genetic abnormalities associated with MDS such as monosomy 7, deletion 5q then it's called AML with MDS related changes.

If the patient didn't meet any of these 4 criteria, then it's called AML, NOS and we revert to the FAB classification. Be familiar with the FAB/WHO classification as it's a commonly tested topic at all levels of training! Treatment depends on the risk. For patients at lower risk of relapse, treatment consists of 4-6 cycles (usually takes 4-6 months) of doxorubicin/ fludarabine based therapy or variations of it. Higher risk patients need to proceed to bone marrow transplant, this includes treatment related AML, AML with MDS like features, any relapsed AML, patients with poor initial response to chemotherapy and others.

3) Chronic myelogenous leukemia: is a stem cell disorder that results in a myeloproliferative neoplasm. The genetic hallmark of this disorder is the Philadelphia chromosome, t (9;22) resulting in the production of the abnormal fusion protein product BCR-ABL1. This disease has three distinct phases:
   A) Chronic phase: most patients are diagnosed in this phase. They can be either asymptomatic or have abdominal pain and distention due to splenomegaly, weight loss, fatigue or night sweats. CBC may show anemia, thrombocytosis, eosinophilia, basophilia. Patients in the chronic phase eventually progress to other phases but latency is very variable.
   B) Accelerated phase: is where clonal evolution starts (one clone starts taking over most of hematopoiesis). During this phase response to treatment (imatinib) usually starts decreasing.
   C) Blast crisis: characterized by the development of acute leukemia that can be either AML or ALL.

   Diagnosis depends on both the clinical feature and detection of Philadelphia chromosome by FISH or the BCR-ABL fusion by PCR. The treatment of choice in the past used to be uniformly a bone marrow transplant but with the advent of the tyrosine kinase inhibitor, imatinib, patients can be put into remission for a prolonged period of time. Resistance can develop to imatinib but there are several alternative now that we can cycle them if resistance develop.

4) Acute lymphoblastic leukemia: it's the most common childhood leukemia with much higher incidence than AML and significantly better overall outcomes. Peak incidence is at age 2-4 years. Some conditions increase the risk for developing ALL. Among these conditions are Down syndrome, immunodeficiencies, Li Fraumeni syndrome (TP53 mutations), Ataxia telangiectasia (T cell ALL and T non-Hodgkin lymphomas), neurofibromatosis, and bloom syndrome. although Down syndrome increases the relative risk for AML more than ALL, ALL remains the most common leukemia in patients with Down syndrome due to its much higher incidence in populations. Another important difference is that while outcomes for AML are very good in patients with Down syndrome, it's the other way around with ALL. About 80% of ALL is of B cell origin and the rest are of T cell origin. High risk features in ALL include T lineage leukemia, age under 1 year at diagnosis or over 10 years, and initial white count over 50,000 WBC / mm3 in addition to high risk genetic mutations. Presenting clinical finings include bone pain, limping, adenopathy, hepatosplenomegaly, mediastinal mass (T cell), and in case of CNS involvement headache, neck pain, seizures and cranial nerve palsies. ALL can involve the testes in males and usually presents with a hard, painless testicular mass. Occasionally X rays are ordered in patients with newly diagnosed ALL due to bone or joint pain any may show osteolytic lesions, osteosclerosis, metaphyseal bands or pathological fractures. The length of treatment for ALL is much longer than for AML and can be up to 3 years. The cornerstone of treatment is chemotherapy with a small subset of patients requiring radiation or stem cell transplant. Typical treatment strategies divide treatment into induction, consolidation and maintenance phases. Typical drugs utilized include steroids, methotrexate, vincristine, asparaginase, mercaptopurine and occasionally anthracyclines for higher risk patients. Overall long-term survival for pediatric ALL these days pushes 90%.

B) Lymphomas:
They can be either B cell derived, or T cell derived and either of these can be mature or immature.

1) Hodgkin lymphoma: perhaps the most famous among lymphomas. It's a mature B cell derived malignancy. By definition, any other lymphoma is a non-Hodgkin lymphoma. Hodgkin lymphomas are more common above the age of 10 years while non-Hodgkin lymphomas are more common under 10 years of age. Factors increasing the risk for Hodgkin lymphoma include affected first degree family members especially sisters, HIV infection, sarcoidosis, ataxia telangectasia and lower socioeconomic status (in adults, higher socioeconomic status is a risk factor). It has 2 main subtypes, classical Hodgkin and nodular lymphocyte predominant Hodgkin. Classical Hodgkin has 5 subtypes, too. We won't describe these types in detail but know that Hodgkin lymphomas are of the classic type and the most common subtype is nodular sclerosing. EBV infections are associated with many vases of HL. The most common presentation is painless lymphadenopathy. A mediastinal mass may be present in about 60-70% of patients on presentation and patients may have constitutional symptoms. Some of the constitutional symptoms predict poor prognosis and these are called the B symptoms (weight loss of 10% on 6 months, night sweats and fever for at least 3 days in a row). Patients usually have elevated acute phase reactants and may present with anemia of chronic disease. HL can be associated with autoimmune disorders including immune cytopenias. Evaluation, in addition to a thorough history and physical exam includes complete counts and chemistries, acute phase reactants, biopsy, CXR, CT of the neck, chest, abdomen and pelvis and a PET scan. Bone marrow testing is indicated for patients with B symptoms and cytopenias. Multiagent chemotherapy and radiation are the cornerstone of HL therapy. Outcomes for low stage disease are excellent. HL treatment increases the risk for secondary cancers in survivors, with the highest increase in relative risk in AML/MDS and the highest cumulative risk in female survivors for breast cancer.
2) Burkitt lymphoma: is a mature B cell lymphoma. This disease is very aggressive in nature but also very responsive to treatment. It has a sporadic and an endemic form. Both can be associated with EBV infections but it's a much stronger correlation with the endemic form. The sporadic form is common in north America and Europe, and usually presents with abdominal mass while the endemic form is common in Africa and usually presents with a jaw mass or abdominal mass. The most common molecular abnormality associated with this tumor is t (8;14).
3) Anaplastic large cell lymphoma: is a mature T cell lymphoma. Can be either localized or systemic. The molecular hallmark is t (2;5) leading to over-expression of the ALK (anaplastic lymphoma kinase).