Chronic myelogenous leukemia

Chronic myelogenous leukemia (CML), also referred to as chronic chronic myelocytic leukemia , may be a cancer of the white blood cells. It's a sort of leukemia characterized by the increased and unregulated growth of myeloid cells within the bone marrow and therefore the accumulation of those cells within the blood. CML may be a clonal bone marrow somatic cell disorder during which a proliferation of mature granulocytes (neutrophils, eosinophils and basophils) and their precursors is found. it's a kind of myeloproliferative neoplasm related to a characteristic chromosomal translocation called the Philadelphia chromosome.

CML is essentially treated with targeted drugs called tyrosine-kinase inhibitors (TKIs) which have led to dramatically improved long- term survival rates since 2001. These drugs have revolutionized treatment of this disease and permit most patients to possess an honest quality of life in comparison to the previous chemotherapy drugs. In Western countries, CML accounts for 15–25% of all adult leukemias and 14% of leukemias overall (including the pediatric population, where CML is a smaller amount common).

Signs and symptoms

The way CML presents depends on the stage of the disease at diagnosis because it has been known to skip stages in some cases. Most patients (~90%) are diagnosed during the chronic stage which is most frequently asymptomatic. In these cases it's going to be diagnosed incidentally with an elevated white blood corpuscle calculate a routine laboratory test. It also can present with symptoms indicative of hepatosplenomegaly and therefore the resulting upper quadrant pain this causes. The enlarged spleen may put pressure on the stomach causing a loss of appetite and resulting weight loss. it's going to also present with mild fever and night sweats thanks to an elevated basal level of metabolism.

Some (<10%) are diagnosed during the accelerated stage which most often presents bleeding, petechiae and ecchymosis. In these patients fevers are most commonly the result of opportunistic infections.

Some patients are initially diagnosed in the blast phase in which the symptoms are most likely fever, bone pain and an increase in bone marrow fibrosis.

Cause

Risk factors

CML is more common in males than in females (male to female ratio of 1.4:1) and appears more commonly in the elderly with a median age at diagnosis of 65 years. Exposure to ionising radiation appears to be a risk factor, based on a 50 fold higher incidence of CML in Hiroshima and Nagasaki nuclear bombing survivors. The rate of CML in these individuals seems to peak about 10 years after the exposure.

Pathophysiology

CML was the first cancer to be linked to a clear genetic abnormality, the chromosomal translocation known as the Philadelphia chromosome. This chromosomal abnormality is so named because it was first discovered and described in 1960 by two scientists from Philadelphia, Pennsylvania, USA: Peter Nowell of the University of Pennsylvania and David Hungerford of Fox Chase Cancer Center.

In this translocation, parts of two chromosomes (the 9th and 22nd) switch places. As a result, part of the BCR ("breakpoint cluster region") gene from chromosome 22 is fused with the ABL gene on chromosome 9. This abnormal "fusion" gene generates a protein of p210 or sometimes p185 weight (p210 is short for 210 kDa protein, a shorthand used for characterizing proteins based solely on size). Because abl carries a domain that can add phosphate groups to tyrosine residues (a tyrosine kinase), the *bcr-abl* fusion gene product is also a tyrosine kinase.

The fused BCR-ABL protein interacts with the interleukin 3beta(c) receptor subunit. The BCR-ABL transcript is continuously active and does not require activation by other cellular messaging proteins. In turn, BCR-ABL activates a cascade of proteins that control the cell cycle, speeding

up cell division. Moreover, the BCR-ABL protein inhibits DNA repair, causing genomic instability and making the cell more susceptible to developing further genetic abnormalities. The action of the BCR-ABL protein is the pathophysiologic cause of chronic myelogenous leukemia. With improved understanding of the nature of the BCR-ABL protein and its action as a tyrosine kinase, targeted therapies (the first of which was imatinib) that specifically inhibit the activity of the BCR-ABL protein have been developed. These tyrosine kinase inhibitors can induce complete remissions in CML, confirming the central importance of bcr-abl as the cause of CML.

Diagnosis

CML is often suspected on the basis of a complete blood count, which shows increased granulocytes of all types, typically including mature myeloid cells. Basophils and eosinophils are almost universally increased; this feature may help differentiate CML from a leukemoid reaction. A bone marrow biopsy is often performed as part of the evaluation for CML, and CML is diagnosed by cytogenetics that detects the translocation which involves the ABL1 gene in chromosome 9 and the BCR gene in chromosome 22. As a result of this translocation, the chromosome looks smaller than its homologue chromosome, and this appearance is known as the Philadelphia chromosome chromosomal abnormality. Thus, this abnormality can be detected by routine cytogenetics, and the involved genes BCR-ABL1 can be detected by fluorescent in situ hybridization, as well as by PCR.

Controversy exists over so-called *Ph-negative* CML, or cases of suspected CML in which the Philadelphia chromosome cannot be detected. Many such patients in fact have complex chromosomal abnormalities that mask the translocation, or have evidence of the translocation by FISH or RT-PCR in spite of normal routine karyotyping. The small subset of patients without detectable molecular evidence of BCR-ABL1 fusion may be better classified as having an undifferentiated myelodysplastic/myeloproliferative disorder, as their clinical course tends to be different from patients with CML.

CML must be distinguished from a leukemoid reaction, which can have a similar appearance on a blood smear.