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Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will **not** issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: **MT00025**.

Each attendee should claim **THREE** CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

DIFFERENTIAL SLIDES LEGEND

CYCLE 38 SLIDE 1

CHRONIC MYELOLOID LEUKEMIA

The chronic leukaemias are distinguished from acute leukaemias by their slower progression. Paradoxically, they are also more difficult to cure. Chronic leukaemias can be broadly subdivided into myeloid and lymphoid groups. The chronic myeloid leukaemias constitute six different types of leukaemia, but by far the most common type is CML associated with the Philadelphia (Ph) chromosome.

Pathophysiology

CML is a clonal disorder of a pluripotent stem cell and is classified as one of the myeloproliferative disorders. The disease accounts for around 15% of leukaemias and may occur at any age. CML was the first malignancy 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 the Fox Chase Cancer Centre at Temple University.

In this translocation, parts of two chromosomes (the 9th and 22nd by conventional karyotypic numbering) 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. 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 which 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 leukaemia. With improved understanding of the nature of the BCR-ABL protein and its action as a tyrosine kinase, targeted therapies have been developed (the first of which was imatinib mesylate) which specifically inhibit the activity of the BCR-ABL protein. These tyrosine kinase inhibitors can induce complete remissions in CML, confirming the central importance of bcr-abl as the cause of CML.

Signs and symptoms

Patients are often asymptomatic at diagnosis, presenting incidentally with an elevated white blood cell count on a routine laboratory test. In this setting, CML must be distinguished from a leukemoid reaction, which can have a similar appearance on a blood smear. Symptoms of CML may include: enlarged spleen causing pain on the left side, malaise, joint and/or hip pain, low-grade fever, increased susceptibility to infections, anemia, and thrombocytopenia with easy bruising (although an increased platelet count (thrombocytosis) may also occur in CML).

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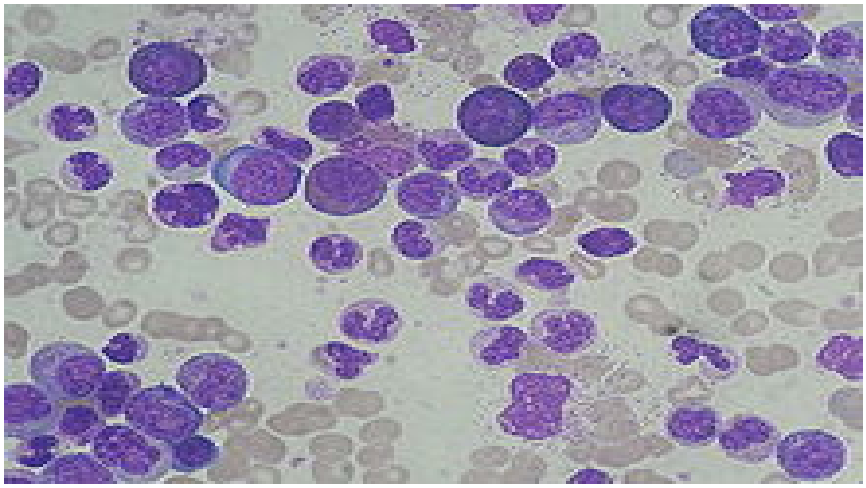
Diagnosis

CML is often suspected on the basis on the 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.



Peripheral blood smear (MGG stain) with marked leucocytosis and a left shift

A bone marrow biopsy is often performed as part of the evaluation for CML, and CML is diagnosed by detecting the Philadelphia chromosome. This characteristic chromosomal abnormality can be detected by routine cytogenetics, by fluorescent in situ hybridization (FISH), or by PCR for the bcr-abl fusion gene.

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 which mask the (9;22) 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-abl fusion may be better classified as having an undifferentiated myelodysplastic/myeloproliferative disorder, as their clinical course tends to be different from patients with CML.

Classification

CML is often divided into three phases based on clinical characteristics and laboratory findings. In the absence of intervention, CML typically begins in the chronic phase, and over the course of several years progresses to an accelerated phase and ultimately to a blast crisis. Blast crisis is the terminal phase of CML and clinically behaves like an acute leukemia. Drug treatment will usually stop this progression if started early. One of the drivers of the progression from chronic phase through acceleration and blast crisis is the acquisition of new chromosomal abnormalities (in addition to the Philadelphia chromosome). Some patients may already be in the accelerated phase or blast crisis by the time they are diagnosed.

Chronic phase

Approximately 85% of patients with CML are in the chronic phase at the time of diagnosis. During this phase, patients are usually asymptomatic or have only mild symptoms of fatigue, left side pain, joint and/or hip pain, or abdominal fullness. The duration of chronic phase is variable and depends on how early the disease was diagnosed as well as the therapies used. In the absence of treatment, the disease progresses to an accelerated phase.

Accelerated phase

Criteria for diagnosing transition into the accelerated phase are somewhat variable; the most widely used criteria are those put forward by investigators at M.D. Anderson Cancer Centre, by Sokal et al., and the World Health Organization. The WHO criteria are perhaps most widely used, and define the accelerated phase by any of the following:

- 10–19% myeloblasts in the blood or bone marrow
- >20% basophils in the blood or bone marrow
- Platelet count <100,000, unrelated to therapy
- Platelet count >1,000,000, unresponsive to therapy
- Cytogenetic evolution with new abnormalities in addition to the Philadelphia chromosome
- Increasing splenomegaly or white blood cell count, unresponsive to therapy

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The patient is considered to be in the accelerated phase if any of the above is present. The accelerated phase is significant because it signals that the disease is progressing and transformation to blast crisis is imminent. Drug treatment often becomes less effective in the advanced stages.

Blast crisis

Blast crisis is the final phase in the evolution of CML, and behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed if any of the following are present in a patient with CML:

- >20% myeloblasts or lymphoblasts in the blood or bone marrow
- Large clusters of blasts in the bone marrow on biopsy
- Development of a chloroma (solid focus of leukemia outside the bone marrow)

Prognosis

A follow-up on patients using imatinib published in the New England Journal of Medicine shows an overall survival rate of 89% after five years.

Epidemiology

CML occurs in all age groups, but most commonly in the middle-aged and elderly. Its annual incidence is 1–2 per 100,000 people, and slightly more men than women are affected. CML represents about 15–20% of all cases of adult leukaemia in Western populations. The only well-described risk factor for CML is exposure to ionizing radiation; for example, increased rates of CML were seen in people exposed to the atomic bombings of Hiroshima and Nagasaki

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References

1. Essential Haematology , edition 4 , AV Hoffbrand, JE Petit, and PAH Moss
2. http://en.wikipedia.org/wiki/Chronic_myelogenous_leukemia

Questions

1. Discuss the Pathophysiology of CML.
2. Discuss the Lab findings in a patient diagnosed with CML.
3. Discuss the classification of CML.
