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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: **MT-11/00142**.

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 41 SLIDE 1

CHRONIC MYELOID LEUKEMIA

Chronic myeloid leukaemia (CML), also known as chronic myelogenous leukaemia, is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. Consequently, the peripheral blood cell profile shows an increased number of granulocytes and their immature precursors, including occasional blasts.

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.

The exact chromosomal defect in Philadelphia chromosome is a translocation. Parts of two chromosomes, 9 and 22, swap places. The result is that a fusion gene is created by juxtapositioning the Abl1 gene on chromosome 9 (region q34) to a part of the BCR ("breakpoint cluster region") gene on chromosome 22 (region q11). This is a reciprocal translocation, creating an elongated chromosome 9 (der 9), and a truncated chromosome 22 (the Philadelphia chromosome). The result of the translocation is the oncogenic BCR-ABL gene fusion, located on the shorter derivative 22 chromosome. This gene encodes the Bcr-abl fusion protein. 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. This action of the BCR-ABL protein is the pathophysiological cause of chronic myelogenous leukaemia.

Clinical features

This disease occurs in either sex (male: female ratio of 1.4: 1), most frequently between the ages of 40 and 60 years. However, it may occur in children and neonates, and in the very old. In most cases there are no predisposing factors but the incidence was increased in survivors of the atom bomb exposures in Japan. Its clinical features include the following:

- Symptoms related to hypermetabolism (e.g. weight loss, lassitude, anorexia or night sweats).
- Splenomegaly is nearly always present and is frequently massive. In some patients, splenic enlargement is associated with considerable discomfort, pain or indigestion.

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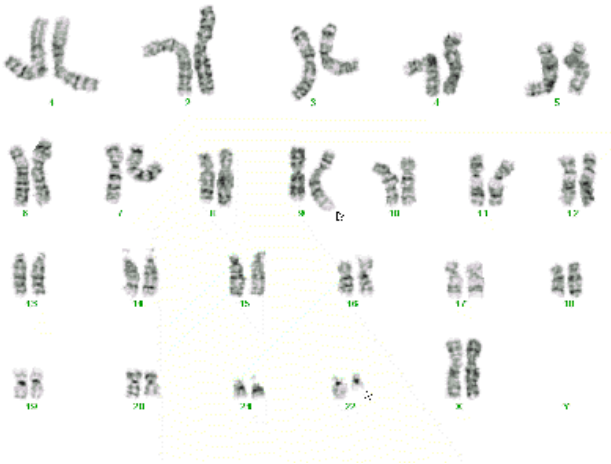
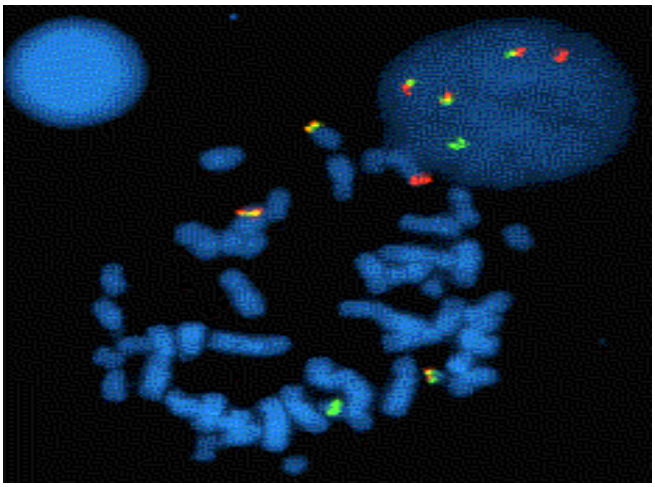
- Features of anaemia may include pallor, dyspnoea and tachycardia.
- Bruising, epistaxis, menorrhagia or haemorrhage from other sites because of abnormal platelet function.
- Gout or renal impairment caused by hyperuricaemia from excessive purine breakdown may be a problem.
- Rare symptoms include visual disturbances and priapism.
- In up to 50% of cases the diagnosis is made incidentally from a routine blood count.

Diagnosis

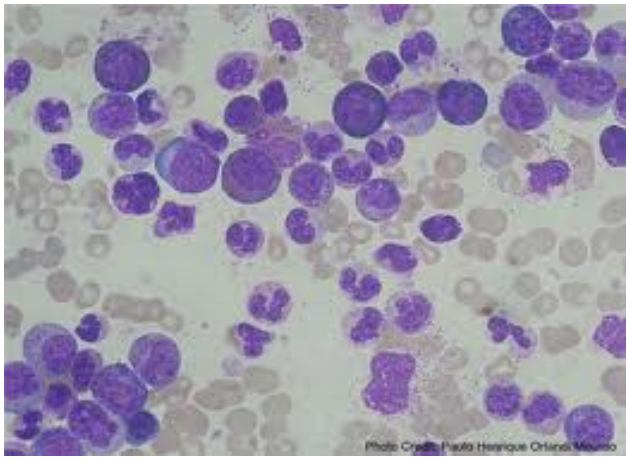
CML is often suspected on the basis of the complete blood count, which shows increased granulocytes of all types, typically including mature myeloid cells. Basophils and eosinophils are almost universally increased; this feature may help differentiate CML from a leukemoid reaction.



Karyotype showing the Philadelphia chromosome.
46,XX,t(9;22)(q34.1;q11.2)



Interphase and metaphase FISH shows gene fusion of BCR (green on chromosome 22) and ABL (orange on chromosome 9). Three fusion (yellow) signals represent one der(9) and two der(22) or Ph chromosomes
Presence of an extra Ph chromosome is a common finding in a blastic phase of CML



Peripheral blood smear with marked leucocytosis

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A bone marrow aspirate and biopsy are essential to quantify the percentage of blasts and basophils, to evaluate the degree of fibrosis, and to retrieve the appropriate diagnostic material for cytogenetic-molecular analyses. The diagnosis of CML is confirmed by finding the Philadelphia chromosome on genetic analysis.

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 leukaemia. 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 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

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.

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Blast crisis

Blast crisis is the final phase in the evolution of CML, and behaves like an acute leukaemia, 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 leukaemia outside the bone marrow)

Prognosis

The prognosis depends on a number of factors like age, phase of CML and extent of splenomegaly. 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.

References

1. Essential Haematology , edition 6 , AV Hoffbrand, JE Petit, and PAH Moss
2. http://en.wikipedia.org/wiki/Chronic_myelogenous_leukemia

Questions

1. Discuss the clinical features of CML.
2. Discuss the lab findings in a patient diagnosed with CML.
3. Discuss the classification of CML.
