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A short review about chronic myeloid leukemia

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Abstract

Chronic myeloid leukemia (CML) develops as a result of a clonal process in a pluripotent stem cell. Anemia, granulocytosis, basophilia, thrombocytosis and splenomegaly are some of the symptoms of the condition. According to clinical findings, the illness progresses through three stages, each of which is identified by a rise in number of the blast cells in peripheral blood or bone marrow: chronic (10%), accelerated (10-19%) and acute leukemia-like blast crisis (20%). Most CML cases could be preliminary diagnosed by the presence of splenomegaly in addition to mutation in the *BCR-ABL* gene as well as complete blood count (CBC) test. Moreover, a bone marrow biopsy can provide a major confirmation of the disease process and staging. Definitive diagnosis of the disease can be either achieved through fluorescence *in situ* hybridization (FISH) or polymerase chain reaction PCR technique.

Keywords: *Chronic Myeloid Leukemia, Philadelphia Chromosome, CML Phases, Diagnosis.*

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I. INTRODUCTION

The bone marrow can normally produce immature blood cells (stem blood cells) which over time develop into mature erythrocyte cells. The blood stem cell has the potential to differentiate into either a myeloid or a lymphoid stem cell. In the process of becoming a leukocyte cell, a lymphoid stem cell divides. The development of myeloid stem cell result in one of three kinds of adult blood cells: red blood cells, white blood cells and platelets (Mondal *et al*., 2014).
Hematological malignancies such as leukemia are classified as diverse groups of diseases in which an abnormally high number of immature white blood cells are created by the bone marrow and other blood-forming organs while simultaneously inhibiting the formation of normal cells in the bloodstream (Gunnarsson, 2017). It was discovered in the 1900s that leukemia may be either acute (progression of the disease rapidly with a large number of immature blast cells) or chronic (progression of the disease slowly with a small number of immature blast cells with more mature-looking cancer cells). On dependence on disease stages, CML can also be classified as myelocytic or lymphocytic (Lyengar *et al*., 2021). Acute leukemia can be further divided into acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). Leukemia of lymphoid and myeloid origin are the two types of chronic leukemia (Meng, 2001). CML is defined as disorder of clonal progenitor of hemopoietic tissue in which there is acceleration in the process of generating new myeloid blast cells with lower rate of apoptosis process. This concomitant with number of symptoms including anemia, fatigue, leukocytosis and splenomegaly in addition to thrombocytosis as well as basophilia. The disease is mainly arise from genetic abnormality involving the formation of philadilphia (Ph) chromosome which result from the translocation in chromosome 9 and 22 long arms t(9;22)(q34;q11.2) which result in the formation of abnormal gene known as *BCR-ABL* that is responsible for the disease pathology (Niederhuber *et al*., 2014).

A. Causes and Pathophysiology

A slow-progressing and clonal myeloproliferative disorder, chronic myeloid leukemia (CML) is the result of neoplastic transformation of the primitive hematopoietic stem cell (HSC), which is monoclonal in heritage and affects myeloid, erythroid, monocytic, megakaryocytic, B-cell, and sometimes T-cell lineages (Fentie *et al*., 2017). Philadelphia chromosome (also known as Ph1 chromosome) (Fig. 1) was firstly mentioned in 1960 by Nowell and Hungerford as the first abnormal chromosome in a malignant disorder. while, in 1973, the chromosomal aberration that responsible for of Philadelphia chromosome

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phenomenon was described as a DNA translocation between chromosomes 9 and 22 (Turgeon, 2012; El Bahy, 2012). Abelson leukemia virus (ABL1) DNA sequences are translocated on chromosome 22 close to the BCR (Breakpoint cluster region) gene. The consequence of the translocation results in the formation of a hybrid oncogene known as BCR-ABL1 (Fig. 1). It is known as p210BCR-ABL1 because it is a fusion gene that codes for or encodes a new oncoprotein of molecular weight 210 kDa, which has been identified as a novel oncoprotein. It has been discovered that this BCR-ABL1 oncoprotein has constitutive kinase activity (Dolinska, 2019; Longo, 2017).

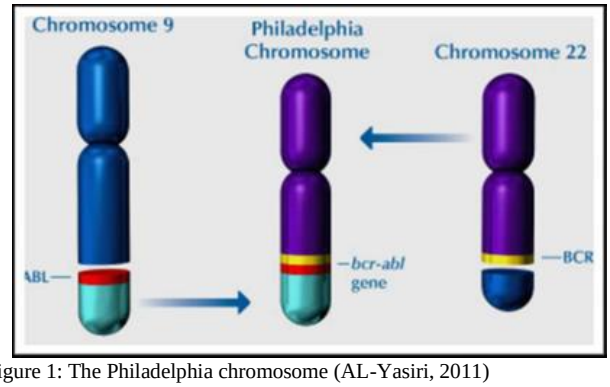

Figure 1: The Philadelphia chromosome (AL-Yasiri, 2011)

In light of the fact that tyrosine kinase ABL controls cell cycle, apoptosis, differentiation and adhesion of hematopoietic cells, the fusion gene BCR-ABL1 has a detrimental effect on LSC proliferation, apoptosis, differentiation and adhesion. Furthermore, when exposed to chemotherapeutic medicines, fusion tyrosine kinase activity alters the response to DNA damage and prolongs the activation of cell cycle checkpoints, extending the time required for DNA repair (Dolinska, 2019).

Reactive oxygen species (ROS) are produced in greater quantities in mitochondria when the BCR-ABL pathway is disrupted. Oxidative DNA damage is caused by an increase in the number of DNA point mutations and double strand breaks, which, in turn, leads to abnormal chromosomal changes as a result of dishonest and incompetent DNA repair processes (Gunnarsson, 2017), in another words, an unstable genome might lead to a rise in medication resistance and cancerous growth (Dolinska, 2019).

There is no actual explanation for this chromosomal translocation, but it is believed to be the result of many chromosomal breaks and repairs happening at the same time during mitosis, which is made easier by the near area of chromosomes 9 and 22 in the interphase nucleus (Fentie *et al*., 2017).

Most patients with CML have the Ph1 chromosome, which is found in myeloid and erythroid precursor cells as well as megakaryocytes. Normal lymphocytes do not normally contain it (Hillman *et al*., 2010; Turgeon, 2012; Longo, 2017).

There may be risk factors that enhance the likelihood of developing the Ph chromosome, which is primarily responsible for the development of CML, even if the reasons remain unclear. CML is thought to be linked to a slew of risk factors. Environmental, chemical, and disease-related risk factors may all contribute to excessive accumulation of Ph chromosomes. By far, radiation, gender, pesticides, and body weight are the primary risk factors for CML (Fentie *et al*., 2017).

People who survived the atomic bomb attack during World War II and those who had radiation treatment for cancers, such as those with ankylosing spondylitis and women with uterine cervical cancer, were more likely to develop CML (and acute leukemia) than those who were not exposed to radiation (Meng, 2001).

Contrary to belief, most occurrences of CML seem to be unrelated to any known risk factors, such as exposure to ionizing radiation (Bollmann *et al*., 2011). Several studies have explored the connection between CML and smoking, and Musselman *et al*. (2013) found only a weak link between CML and current smokers (1 pack/day) as compared to controls. However, other studies have failed to find any connection between CML and smoking (Gunnarsson, 2017).

It was found that there is no familial association with CML. Furthermore, monozygotic twins and patients' relatives do not have an elevated chance of acquiring CML. No etiologic agents are implicated, and there are no correlations with viral exposures (Longo, 2017). In addition, CML does not seem to have any hereditary causes (Meng, 2001; El Bahy, 2012, Söderlund, 2017). Prior to being diagnosed with CML, participants in the Swedish CML registry had a higher frequency of various malignancies and autoimmune illnesses, showing that their heightened propensity to cancer and autoimmunity is either hereditary or acquired (Söderlund, 2017).

HLA antigens, CW3 and CW4 may also be linked, according to study by Boylu, 2004. Certain HLA types have been shown to protect against the development of CML in individuals who express HLA-B8, HLAA3 and HLA-DR4 (El Bahy, 2012).

B. Stages and symptoms

The World Health Organization (WHO) classifies CML as three distinct phases: the chronic phase (CP), then the accelerated phase (AP) and finally the blast phase (BP) (AL-Yasiri, 2011; Lavrov *et al*., 2016; Kuan *et al*., 2018). When CML moves from the chronic phase to the more aggressive accelerated phase (AP), it becomes more difficult to manage the illness. The accelerated phase (AP) is an indication of advancement and change into the generally fatal blast phase (BP) (Furtado *et al*., 2015). It is estimated that around 20% of patients undergo a shift from CP to BP without the presence of AP warning signs (Jabbour and Kantarjian, 2018).

C. Chronic phase of CML

The diagnosis of most patients with CML occur during the chronic phase (CP) of disease, with about 20% and 45% of them being asymptomatic at the time of diagnosis (Navas *et al*., 2010; Bollmann *et al*., 2011). The reason is that CML

patients in the chronic phase have immunity of a normal healthy person and may go for extended periods of time without showing any signs of illness (Quintás-Cardama and Cortes, 2006). As soon as they become symptomatic, these patients will show signs of hyper-catabolism (fatigue, night sweats, lack of appetite and fever), as well as abdominal pain caused by spleen enlargement (splenomegaly). Fewer than 5% of CP cases will show bleeding or thrombotic complications, according to the American Heart Association (Bollmann *et al*., 2011).

In the chronic phase, the median of overall survival (OS) is more than five years (Navas *et al*., 2010). A leukocytosis will be seen on the peripheral blood smear owing to the presence of granulocytes at varying stages of maturation. An asymmetric bimodal distribution will be seen, with larger proportions of mature segmented neutrophils and myelocytes than in the undifferentiated state. Increased basophils and eosinophils are prevalent in this situation. There is no evidence of significant dysplasia in which >10% of granulocyte population have been affected. The presence of monocytosis is possible; although, it is > 3 % of the total number of white blood cells (Fig. 2). Platelets are often seen in a range between the normal range and a considerable increase. Thrombocytopenia is a rare complication of the disease (Eden and Coviello, 2021). Patients presenting in the chronic phase have blasts in their bone marrow and blood in a proportion of 10% (Hamad, 2019).

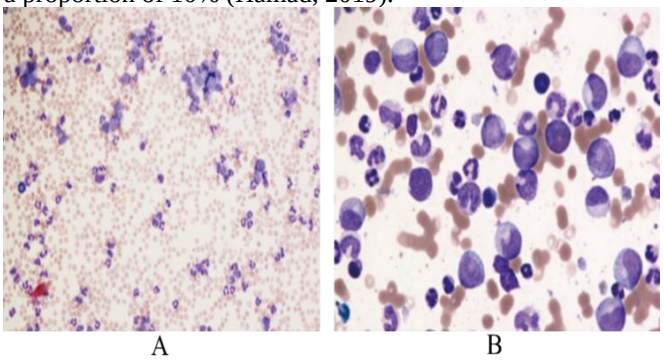

Figure 2: A. Peripheral blood of CML-CP patient showing leukocytosis and circulating immature myeloid cells (Wright_Giemsa stain, ×4). B. Bone marrow aspirate of CP-CML patient showing a range of immature myeloid cells-including blast cells and promyelocytes (Wright_Giemsa stain, ×20) (Granatowicz *et al*., 2015).

An aspirate and biopsy from the bone marrow will reveal hypercellularity, with considerable granulocytic proliferation and considerably enlarged myelocytes, albeit there should be no sign of severe dysplasia in the sample. Megakaryocyte count may be decreased, normal, or augmented depending on the situation (Eden and Coviello, 2021).

There is currently no known cause for the shift from CP to the late stages of the illness; nevertheless, genomic instability is suspected to be a contributing factor. Cell proliferation mediated by BCR-ABL would cause additional chromosomal abnormalities in the tumor cells, which is known as clonal evolution, (Bollmann *et al*., 2011).

D. Accelerated phase of CML

In the accelerated phase (AP), which can last anywhere from a few weeks to several years (Boylu, 2004), the existence of one or more of the following features is required: fewer than 15% blasts in peripheral blood/BM, fewer than 20% basophils in peripheral blood, platelets fewer than 105/L unrelated to the development of cytogenetic evolution or treatment (Fig. 3) (Lavrov *et al*., 2016). CML-AP may be subtle, or it might manifest as increasing anemia, splenomegaly, and organ infiltration (Jabbour and Kantarjian, 2018), as well as fever and weight loss among other symptoms (AL-Yasiri, 2011). It takes between 1 and 2 years to reach the end of life for people with CML-AP. The majority of patients' CML will stay in the acute phase for 4 to 6 months before moving to the chronic phase (Russo *et al*., 2020).

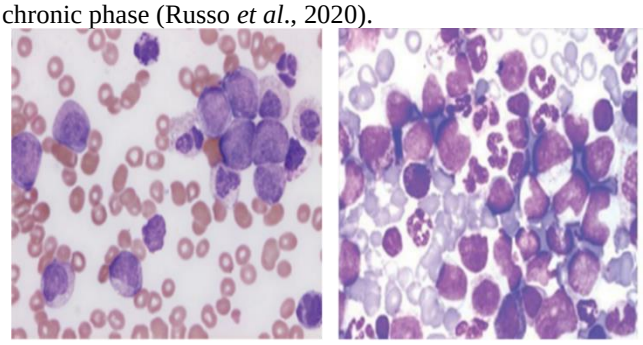

Figure 3: A. Peripheral blood smear of CML (Accelerated phase): showing basophils, myeloblasts, and thrombocytopenia. B. Accelerated phase of CML: smear of bone marrow aspirate showed megakaryocytes and myeloid cells with massive blasts cells (MGG-Giemsa stain, x1000) (Kumar *et al*., 2013).

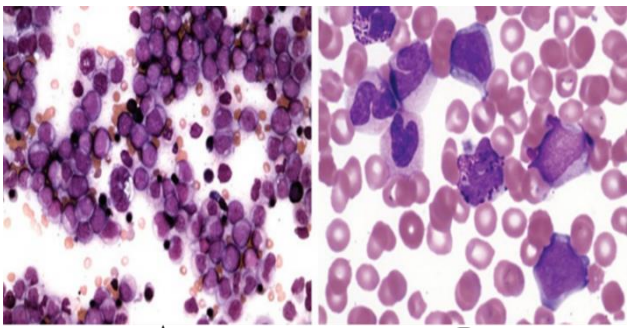

Figure 4: Smears of bone marrow (A) and peripheral blood (B) of a patient with CML in blast transformation shows abundant blasts with a few basophils cells (Naeim *et al*., 2018).

E. Blast phase of CML

In the blast phase, anemia is more common and more than 30% of blasts are present in either the peripheral blood or the bone marrow with clusters of blasts in marrow or the presence of extramedullary illness with immature cells (Fig. 4) (Lavrov *et al*., 2016). Proliferation outside of the medullary cavity is most typically observed in the skin, bone, lymph nodes and the central nervous system (CNS) (Eden and Coviello, 2021). Chronic myeloid leukemia-BP manifests as an acute leukemia (myeloid- in 60% of cases, lymphoid- in 30% and megakaryocytic or undifferentiated-

in 10%) accompanied by deteriorating constitutional symptoms (Jabbour and Kantarjian, 2018). Many of the signs and symptoms associated with high tumor burden are experienced by the majority of patients with CML-BP, including difficulties in controlling leukocyte counts with previously stable drug doses, severe constitutional symptoms (anorexia, fever, night sweats, malaise and weight loss), bone pain, splenic infarcts as a result of massive splenomegaly, as well as an increased risk of infection and bleeding (Quintás-Cardama and Cortes, 2006). During this time span, the typical survival time is 3-6 months (Hamad, 2019; El Bahy, 2012). In untreated individuals, progression to BP requires at least 3–5 years after diagnosis, whether or not there is an intervening identifiable factor (Lavrov *et al*., 2016).

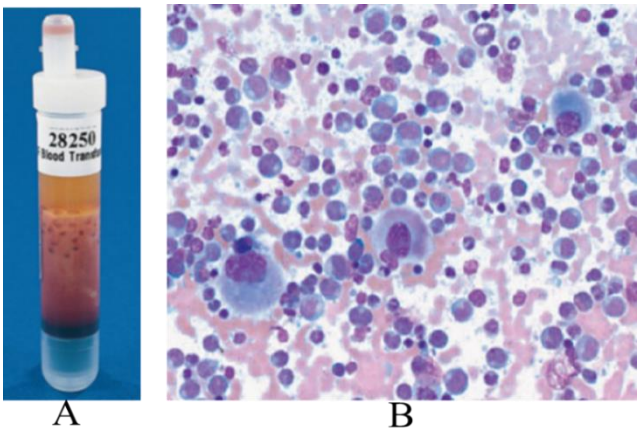

Figure 5: A. A Peripheral blood from 22-year-old woman suffering from Chronic myeloid leukemia showed an abnormal massive increase in buffy coat. (WBC, 532 × 109/L; Hb, 6.1 g/dL; platelets, 676 × 109/L) (Hoffbrand *et al*., 2019). B. CML- Characteristic granulocytic proliferation and "Dwarf megakaryocytes" (Wright-Giemsa) (Vardiman, 2009)

II. Diagnosis

It is usually straightforward to determine whether a patient has CML. Typically, blood total count and differential count may be used to make the diagnosis in almost all circumstances (Hochhaus *et al*., 2017). The following are the characteristics of a typical complete blood count (CBC): Absolute basophilia is almost universal, and is present in nearly 90 % of cases. The vast majority of patients have absolute leukocytosis (median of 105/L; Fig. 5 A) with a left shift and classic "myelocyte bulge" (more myelocytes than the more mature metamyelocytes seen in the blood film); blasts account for < 2 % of the total; absolute leukocytosis (Quintás-Cardama and Cortes, 2006; Thompson *et al*., 2015,). Though monocytosis is frequently seen, high percentage of monocyte is seldom observed; absolute monocytosis is more evident in the rare instances of p190 BCR-ABL (Thompson *et al*., 2015). which is associated with a p190 BCR-ABL mutation. Megakaryocytes may range in size and form from somewhat reduced to much expanded, and they can exhibit distinctive characteristics (for example, dwarf megakaryocytes are smaller and have hypolobated nuclei; Fig. 5 B) (Quintás-Cardama and Cortes, 2006; El Bahy, 2012). The considerable increase in WBC pool size is associated with an elevation in the serum level of B12 along with unsaturated B12 binding capacity. The level of circulating basophil, histamine, or both are often raised during the transition to CML-BP; although, the underlying reasons and significance of these events remain unknown (Quintás-Cardama and Cortes, 2006). Untreated CML is characterized by an elevated generation of uric acid, as well as hyperuricemia and hyperuricosuria (Kaushansky *et al*., 2016).

The presence of Philadelphia (Ph) chromosome, 22q or BCR–ABL1 transcripts (or both) in bone marrow cells or peripheral blood are used to confirm the diagnosis of CML (Guo *et al*., 2002; Hochhaus *et al*., 2017). Fluorescence in situ hybridization (FISH) or the reverse transcriptase-polymerase chain reaction (RT-PCR) confirmation of the BCR–ABL1 fusion is required in 5% of patients, and in 18% of cases, the Ph chromosome cannot be found, therefore the diagnosis must be confirmed by other methods, such as reverse transcriptase polymerase chain reaction (Hochhaus *et al*., 2017). The co-localization of large genomic probes unique to the ABL and BCR genes is the foundation of a FISH study. High concordance was found when FISH technique was used to compare marrow and blood samples simultaneously. There may be a 1-5% false positive rate in FISH investigations, depending on the probes used. The splice junction between the BCR and ABL1 is amplified by RT-PCR. It has a good sensitivity for identifying a little amount of illness after treatment. Tests for BCR-ABL1 transcripts may be qualitative (QPCR), indicating the existence of the transcript, or quantitative (QC), measuring the quantity of transcripts present. CML may be diagnosed by qualitative PCR, whereas quantitative PCR is best for tracking the progression of the illness (Jabbour and Kantarjian, 2018). Southern blotting and Western blotting may be employed to identify the Bcr-Abl oncoprotein in the breakpoint cluster region of the BCR gene (Guo *et al*., 2002).

No Ph chromosome or BCR–ABL1 rearrangement may be seen in some CML patients who have symptoms and signs of the illness. The World Health Organization (WHO) classifies these individuals as having Philadelphia-negative (Ph_) and BCR–ABL1 negative CML, or as having atypical CML (Hochhaus *et al*., 2017; Gunnarsson, 2017).

III. Epidemiology

Chronic myelogenous leukemia (CML) represents 15% of all adult leukemias, with less than 10% of cases appearing in children under the age of 20 years (Bollmann *et al*., 2011). According to extrapolation, the incidence of CML around the globe is around 100,000 cases/ year (Longo, 2017). Men are more likely than women to be diagnosed with CML, which has a frequency of 1: 2 cases/100,000 persons (Faderl *et al*., 1999; Gunnarsson, 2017; Jabbour and Kantarjian, 2018), with 1.3: 1 male to female ratio. The likelihood of contracting the disease rises with age. The typical age at presentation ranges from 45 to 55 years, while other series

show a median age as high as 67 years in rare instances (Faderl *et al*.,1999; Bollmann *et al*., 2011). Despite some reports of reduced incidence rates in certain Asian communities impacting the younger populations (Hamad, 2019), there is no convincing evidence to imply that any specific ethnicity is more likely to be affected. In Western countries, the typical age of CML patients has been reported to be 65, however, in Asian countries; the median age of CML patients has been discovered to be between 36 and 50 years old. (Mjalia and Abbas, 2021). A study conducted in Iraq between 2002 and 2006 revealed that the median age was 37 years old. Males are more likely than females to be affected (Alameri *et al*., 2009). No such concordance exists between identical twins when it comes to this illness (Meng, 2001).

IV. CONCLUSIONS

In conclusion, CML is a slowly developing malignant disorder of the hemopoietic tissue. Therefore, early diagnosis gives a better outcome, and regular screening test, especially in suspected families is mandatory to control the disease and alleviate the consequences of the CML with increasing the chance of recovery in patients after treatment.

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