Original article

Clinicopathological features of chronic myeloid leukemia at diagnosis: Study of a series of 46 cases

Shittu AO1, Babatunde AS2, Adewoye AO3

Abstract:

Introduction: A variety of symptoms and signs are said to be common at diagnosis of chronic myeloid leukemia, but their exact incidence is not well documented. There are conflicting opinions on the incidences of the symptoms and signs. Subjects and methodology: This is a retrospective study whereby the clinical and laboratory features of 46 patients diagnosed as chronic myeloid leukemia at different phases between 1999 and 2009 were retrieved from their case files and analyzed. Results: Of all the patients, 38, 6 and 2 presented in chronic, accelerated and blastic phases respectively. The mean age of the series was 38.3 years (range 17-68 years). The peak age of presentation was 31-40 years (30.48%) followed by 21-30 years (26.1%), 41-50 (21.7%), above 50 years (17.4%) and 10-20 years (4.3%). There was a slight male preponderance 24:22 (1.09:1) with 65% of patients being married and 35% single. Occupation wise, the ratio of petrochemical and benzene related jobs to others was 3:43 (0.07:1). Splenomegaly was the commonest presenting clinical feature in this series and was reported in 44 (95.6%) of our patients. Others were anemia, weight loss, fever, hepatomegaly and night sweat. Conclusion: Because of unavailability and unaffordability of the sophisticated diagnostic tools like quantitative PCR in developing worlds, there is need for clinicians to be up to date with the usual and common clinical and laboratory features of chronic myeloid leukemia.

Keywords: chronic myeloid leukaemia; clinicopathological features; Ilorin; Nigeria

Introduction

Chronic myeloid Leukemia (CML) is a clonal disorder resulting from an acquired genetic abnormality in a multi-potential haemopoietic stem cell. These altered stem cells proliferate and generate a population of differentiated cells that gradually displaces normal haemopoiesis and leads to a greatly expanded total myeloid cells. The discovery of the Philadelphia chromosome (Ph) in 1960 and the characterization of the BCR-ABL chimeric genes, an associated oncoproteins in 1980, are important landmarks in the study of CML1.

The disease has features of leucocyte hyperplasia at all stages of differentiation. It is seen predominantly among adults, with the median age at diagnosis ranging widely between 35 and 60 years2-4,10. It constitutes less than 10% of all Leukaemias seen under the age of 20years4, and 7-20% of all Leukaemias cases seen at all ages5. It is very rare after the age of 60 years and occasionally occurs in children11. The disease constitutes about 11.4% of all haematological cases seen here at our center, Ilorin, Nigeria6. There is a slight male preponderance in most studies with ratio of 1.4:17,8, but a female preponderance among elderly with Philadelphia positive cases have been reported9. Its incidence ranges between 10-15 cases/106/year (age adjusted) without any major geographic or ethnic differences11. The disease has two or three phases – the chronic phase, the phase of acceleration and the blastic phase. Eighty five percent of all the patients are diagnosed in chronic phase and about 40% of them are asymptomatic5. The rest are diagnosed in the accelerated and blastic phases. The median age at diagnosis ranges between 60 and 65 years in Europe but very low in countries where the population is younger12 with median survival from the time of diagnosis of approximately

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Clinicopathological features of chronic myeloid leukemia

4 years with conventional chemotherapy of busulfan or hydroxyurea\textsuperscript{1,3}, but much longer now with the introduction of tyrosine kinase inhibitors (Imatinib mesylate, Dasatinib and Nilotinib) in the management.

A variety of symptoms and signs are said to be common at diagnosis of chronic myeloid leukaemia, but their exact incidence is not well documented\textsuperscript{13,14} There are conflicting opinions on the incidences of the symptoms and signs. The most frequent presenting clinical features are fever\textsuperscript{13}, bleeding\textsuperscript{15}, fatigue due to anaemia, weight loss and splenomegaly\textsuperscript{16}.

Although the confirmation of diagnosis of chronic myeloid leukaemia is the demonstration of cytogenetic abnormality called Philadelphia chromosome or its molecular equivalent (BCR-ABL fusion) by Polymerase Chain Reaction (PCR), the hallmark of diagnosis is demonstration of leukocytosis with basophilia, immature granulocytes, mainly metamyelocytes, myelocytes, promyelocytes and few or occasional myeloblasts in the peripheral blood\textsuperscript{12}. Bone marrow aspiration findings and clinical features will support the diagnosis. Cytogenetic studies are not available in most centers in developing countries like ours. At the centers where they are available, the cost is prohibitive to most of our patients. There is therefore the need to be conversant with the usual clinical features, peripheral blood film and bone marrow aspiration findings in this environment.

**Objective of the study:**
Cytogenetic studies with the demonstration of Philadelphia chromosome is the hallmark of diagnosis and management of CML. Because of the unavailability and unaffordability of these studies by most of our patients, there is need to be familiar with the common and the usual clinical and laboratory features of this common disorder in our environment.

**Materials and methods**

**Study Area:**
This study was conducted at University of Ilorin Teaching Hospital, a tertiary health center located at Ilorin, the capital of Kwara state. The hospital serves Ilorin and the suburb villages with a total estimated population of about 2,591,555 people\textsuperscript{17}. Heamatological cases are seen and managed at the Haematology and Blood Transfusion Department of the hospital. Referral cases from other parts of the country were also seen at the hospital. Ethical approval was taken before the study from ethical Committee of University of Ilorin Teaching Hospital.

**Materials:**
The study was a retrospective one whereby case files of all subjects diagnosed with CML in the period 1999 to 2009 were retrieved from medical and health records department of the hospital.

During the study period, 46 patients were seen and diagnosed as CML in chronic, accelerated and blastic phases. The following parameters were extracted from the case files: age, sex, occupation, marital status, clinical symptoms like fever, weight loss, fatigue, tiredness, pain, swelling and night sweat, clinical signs like palor, lymphadenopathy, splenomegally, hepatomegally, skin charges and then laboratory features like PCV, total WBC counts and its differentials (Blasts, promyelocytes, myelocytes, metamyelocytes, band neutrophils, mature neutrophils, eosinophils and basophils) and platelet counts.

All the subjects diagnosed between 1990 and 2005 had no cytogenetic studies done because of its non-availability in the country then but those diagnosed after 2005 had karyotyping done at Obafemi Awolowo University Teaching Hospital, another teaching hospital in the South West region of the country.

Criteria for the diagnosis of CML in chronic phase were persistent leucocytosis >50 x 10\(^9\)/L, WBC differential showing neutrophilia with immature myeloid cells (blast less than 10%), basophilia and eosinophilia, high or low platelet count, absence of secondary cause/s of leucocytosis and massive splenomegally with or without any of the constitutional symptoms like fatigue, fever, night sweat, weight loss etc. Chronic myeloid leukemia in accelerated phase was defined when there is very rapid leukocyte doubling time, leukocyte count resistant to control with busulphan or hydroxyurea, anaemia or thrombocytopenia despite adequate chemotherapy, more than 12% blast in peripheral blood etc. while blastic phase was defined as blast count in the peripheral blood more than 20%. Anaemia was defined as haemoglobin concentration less than 11.5g/dl for women and less than 13.5g/dl for men. Fever was defined as body temperature greater than 37\(^0\)c, weight loss as reduction in weight as evidenced by looseing of cloth, shoes, belt etc, hepatomegally or splenomegally when liver and spleen were palpable below the right or left costal margin respectively. Night sweat was defined as a drenching of night cloth/ pyjamas by sweat.

The data was analyzed using SPSS version 2.0. Continues variables were analyzed as means
Results:

At the time of diagnosis, 38 patients (82.6%), 6 patients (13%) and 2 patients (4.3%) presented in chronic, accelerated and blastic phases respectively, Figure 1. And Table 1 shows the clinical features of all patients.

![Figure 1: Phases of Chronic Myeloid Leukaemia in the subjects.](image)

<table>
<thead>
<tr>
<th>Features</th>
<th>Number/Percentage of Patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>AGE (YEARS):</td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>2(4.3)</td>
</tr>
<tr>
<td>21-30</td>
<td>12(26.1)</td>
</tr>
<tr>
<td>31-40</td>
<td>14(30.4)</td>
</tr>
<tr>
<td>41-50</td>
<td>10(21.7)</td>
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<tr>
<td>&gt;50</td>
<td>8(17.4)</td>
</tr>
<tr>
<td>SEX</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24(52.2)</td>
</tr>
<tr>
<td>Female</td>
<td>22(47.8)</td>
</tr>
<tr>
<td>FEVER</td>
<td>28(60.9)</td>
</tr>
<tr>
<td>ANAEMIA</td>
<td>38(82.6)</td>
</tr>
<tr>
<td>WEIGHT LOSS</td>
<td>30(65.2)</td>
</tr>
<tr>
<td>SPLENOMEGALLY</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>44(95.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4(8.7)</td>
</tr>
<tr>
<td>Massive</td>
<td>8(17.4)</td>
</tr>
<tr>
<td>HEPATOMEGALLY</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>26(56.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>6(13)</td>
</tr>
<tr>
<td>Massive</td>
<td>18(39.1)</td>
</tr>
<tr>
<td>NIGHT SWEAT</td>
<td>10(21.7)</td>
</tr>
</tbody>
</table>

The mean age of the series was 38.3 years (range 17-68 years). The peak age of presentation was 31-40 years (30.48%) followed by 21-30 years (26.1%), 41-50 (21.7%), above 50 years (17.4%) and 10-20 years (4.3%). There was a slight male preponderance 24:22 (1.09:1) with 65% of patients being married and 35% single. Occupation wise, the ratio of petrochemical and benzene related jobs to others was 3:43 (0.07:1).

Spleneomegally was the commonest presenting clinical feature in this series and was reported in 44 (95.6%) of our patients. Others were anaemia, weight loss, fever, hepatomegally and night sweat which were seen in 38 (82.6%), 30 (65.2%), 28 (60.9%), 26(56.5%) and 10 (21.7%) patients respectively. For splenomegally, 32(69.6%), 8(17.4%) and 4(8.7%) patients presented with massive, moderate and mild form respectively, while massive, moderate and mild hepatomegally were seen in 2 (4.3%), 18 (39.1%) and 6 (13%) of patients respectively.

The mean haemoglobin concentration in the series was 7.3g/dl with the range of 4-13.3g/dl. Thirty eight (82.7%) and 8(17.3%) patients had haemoglobin concentration less and greater than 10g/dl. All patients had neutrophil leucocytosis with total WBC count greater than 20 x 10⁹/L and with the mean of 167.8 x 10⁹/l. Ten (21.7%), 18(39.1%), 16(34.7%), and 2(4.3%) had ranges of less than 100x 10⁹/l, 100-200 x 10⁹/l, 201-300 x 10⁹/l, and greater than 300 x 10⁹/l respectively. None of the patients presented with features of hyperleucocytosis. The mean platelet count was 153.7 x 10⁹/l. Platelet count was normal in 28(61%) while thrombocytopenia and thrombocytosis were seen in 12(26%) and 6(13%) of patients.

Thirty eight (82.6%), 6(13%) and 2(4.3%) patients had blasts differential counts of less than 10%, 10-19% and >20% respectively. For the
other differentials, promyelocytes, myelocytes, metamyelocytes and band neutrophils of greater and less than 10% were seen in 38(82.5%) and 4 (17.4%), 12(26.1%) and 34(73.9%), 4(8.7%) and 42(91.1%) and 6(13%) and 40 (87%) respectively. Segmented neutrophil differential count greater and less than 50% was recorded in 18(39.1%) and 28(60.9%) of patients. Basophils, eosinophils and monocytes counted together as others was less than 2% in 38(82.5%) and 2-5% in 4(17.4%) of patients. Lymphocyte counts less and greater than 20% were recorded in 40(87%) and 6(13%) of our patients respectively. Table 2 and 3 shows the PCV, Total WBC & Platelet counts and differential counts of all the patients

Discussion:
Although the hallmark of diagnosis of CML is the cytogenetic demonstration of Philadelphia chromosome or its equivalent, BCR/ABL fusion, all our patients were diagnosed based on clinical, peripheral blood and bone marrow findings. Our findings suggested that CML in our region have similar characteristics with those in other African regions and the western world.

Chronic myeloid leukemia is a disorder that usually progresses from a chronic indolent phase through an accelerated phase to a rapidly fatal blast phase. All the phases were represented in this series, despite the small number of cases seen in the study period. Most patients in the series, 82.6%, were diagnosed in chronic phase with clinical features of moderate splenomegally, anaemia and fever, as compared with 72.6% and 78.6% by other authors. The median age of presentation in this series was 38 years, similar to that earlier reported in Nigeria, with male preponderance as documented by most authors but not all authors. The calculated annual incidence in this series was 1.8 cases/10⁶/year which is far below that reported in other countries. This could be attributed largely to poor hospital attendances of our people and therefore gross under reporting of this disease. Splenomegally, similar to other report, was the commonest clinical feature in this study followed by anaemia, weight loss, fever, hepatomegally and night sweat.

The low mean haemoglobin concentration found in this series was similar to the findings of some but lower than that of other authors. Markedly raised total WBC counts (>100 x 10⁹/l) was common in this series (mean of 167.8 x 10⁹/l), similar to the findings in other studies, but complications arising from leucostasis like priapism, retinopathy, deafness and mental disturbances were not seen. This is because the syndrome of leucostasis is more common in the blast phase because of large and rigid blast cells in peripheral blood. In our series, very few, in fact only two patients were seen in blast phase. Most of our patients presented with normal platelet counts (90-300 x 10⁹/l), similar to report by other authors where the count was found to be normal but different from others that reported thrombocytosis or thrombocytopenia.

Few reports are available concerning WBC differential counts in CML in this environment. Hence our findings could serve as baseline for other researchers.

Conclusion:
Although this is a retrospective study with limited number of patients, our findings are similar to that found by previous researchers. These findings could be of great benefit to physicians and haematologists in developing countries who do not have access to sophisticated diagnostic tools like Quantitative PCR and FISH to demonstrate the BCR/ABL fusion genes in chronic myeloid leukaemia.
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