

Evaluation of the Clinico-haematological Characteristics and Pattern of Presentation of Acute Myeloid Leukemia in Ilorin, North Central Nigeria

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Abstract

Acute myeloid leukemia (AML) is a malignant haematological disorder of the myeloid lineage in the bone marrow resulting from clonal proliferation of haemopoietic progenitor cells with accumulation of myeloblasts in the blood, bone marrow and tissue infiltration. The aim of this retrospective study was to determine the pattern of presentation, clinical features and haematological parameters of AML patients diagnosed at the Haematology Department of U.I.T.H, Ilorin between 1st January 2008 and 31st December 2018. The study materials included Bone marrow registers from the department and case folders of all AML patients diagnosed within the study period. Relevant data including socio-demographic characteristics of patients, clinical features at presentation and laboratory tests results were extracted, documented and analyzed. Diagnosis of AML was made based on the findings of ≥ 20% blasts in the bone marrow and/or peripheral blood and classified using FAB classification criteria. There were forty-six patients and their median age at diagnosis was 20.6 ± 15.9 years. The highest prevalence of the disease was found in the 11 – 20 years age group. The most common presenting symptoms were fever (91.3%), pallor (84.8%), bleeding diathesis (52.2%), and body weakness (45.7%). The mean ± SD values of haematological parameters in the patients were – PCV (19.9 ± 5.8%), Hb conc. (6.6 ± 1.9 g/dL), Total WBC (48.1 ± 54.8 × 10⁹/L) and Platelet Count (39.6 ± 24.0 × 10⁹/L). The commonest subtype of AML in our study was M4 which was seen in 26 (56.5%) patients, followed by M5 observed in 10 (21.7%) patients. In resource-limited settings such as ours, the diagnosis and monitoring of patients with AML still rely on the clinical and laboratory features of the disease to a large extent, hence the need for Haemato-oncologists and Physicians to be conversant with these features.

Keywords: Acute myeloid leukemia, clinical features, haematological, parameters, Ilorin

Introduction

Acute leukemias (AL) are a heterogeneous group of haematological neoplasms of the haemopoietic progenitor cells of the bone marrow which are characterized by excessive abnormal proliferation and accumulation of malignant, immature white blood cells in the bone marrow, peripheral blood and various tissues¹.

Acute leukemias are divided into two main morphological types – Acute myeloid leukemia (AML) and Acute lymphoblastic leukemia (ALL) based on the type of white blood cells involved. They are clonal neoplasms which are

induced by genetic damage or mutation in haemopoietic progenitor cells from environmental agents such as chemicals, ionizing radiation or viral agents and are often associated with fundamental genetic and molecular abnormalities².

Acute myeloid leukemia is a malignant haematological disorder which results from clonal proliferation of myeloid precursors in the bone marrow with excessive abnormal accumulation of immature white blood cells (myeloblasts) in blood, bone marrow, various organs and tissues³.

The most common clinical features which are observed in patients with AML at presentation are mainly due to the excessive accumulation of the myeloblasts in the bone marrow with suppression of haemopoietic activities thereby resulting in bone marrow failure and paucity of

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matured red blood cells and platelets in circulation, functional neutropenia, infiltration of various tissues and organs by the leukemic cells; and the hypermetabolic state from increased cell turnover. These include fever, anaemia, infections, bleeding diathesis, body weakness, pallor, hepatomegaly, splenomegaly, lymphadenopathy and gum hypertrophy⁴. The pattern of clinical presentation is variable and depends to a large extent on the nature and extent of disease, sex and age of patients at presentation and presence of cytogenetic abnormalities at diagnosis.

Acute myeloid leukemia has a worldwide distribution and is known to occur at all ages and in both sexes but with a male preponderance. In the Western countries, AML accounts for about 30% of all leukemias in adults above 60 years of age, and is more common in males than females with a Male: Female ratio of 2.5:1^{1,5}, but some other studies have reported higher prevalence in much younger age groups^{6,7}. In Ibadan, Nigeria, the annual incidence of AML had been reported to be 1.9 per 10⁶ per year⁸. Acute myeloid leukemia was also reported to be the commonest form of acute leukemias in Ethiopia, constituting 63.8% acute leukemia cases studied⁹. A previous study in Ilorin, Nigeria, reported that Acute myeloid leukemia constituted 12.7% of all cases of haematological malignancies, and 57.5% of acute leukemias² and also, in India, Ramprasanth et al³ reported AML in 55% of patients with leukemias in their study.

Diagnosis of AML is often made based on morphology, cytochemistry, cytogenetics and immunophenotyping while classification is made using FAB or WHO Working Party criteria^{10, 11}. In many centres in Nigeria, and other resource limited settings, cytogenetics and molecular methods of diagnosis are not readily available, or the high costs make them unaffordable to majority of patients, so diagnosis of Acute myeloid leukemia is still made to a large extent based on the clinical features at presentation and routine full blood counts and bone marrow examinations.

It is therefore imperative for haematologists and other clinicians in our centres within Nigeria and in other resource limited settings to be conversant with the clinical features and haematological profile of the disease which are still being commonly used in the diagnosis and management of patients with Acute myeloid leukemia.

The aim of this study, therefore, is to describe the pattern of presentation and the clinical and laboratory features of patients with diagnosis of Acute myeloid leukemia at the University of Ilorin Teaching Hospital, Ilorin, north central

Nigeria, and compare our findings with reports from other centres within and outside Nigeria.

Materials and Methods

This study was a retrospective review of all cases with diagnosis of AML which were seen and managed at the Department of Haematology and Blood Transfusion, University of Ilorin Teaching Hospital (UITH), Ilorin between 1st January 2008 and 31st December 2018 inclusive. The UITH is a 650 bedded tertiary health institution located in Ilorin, North central geo-political zone of Nigeria. It serves as a referral center for neighboring states of Oyo, Osun, Ekiti, Kogi and Niger states of Nigeria. Ilorin, the capital city of Kwara State, Nigeria, is located on the latitude 8.5° North and longitude 4.55° East with a total population of 908,490 and an annual growth rate of 2.3%¹².

The Haematology department of U.I.T.H is involved in the investigations, clinical evaluation and management of blood and blood related disorders. It also carries out laboratory services, interpretation of laboratory test results and receives consultations from other clinical departments of the hospital.

The materials used for this study were data obtained from patient's case folders. The case folders of all the patients that were included in our study were retrieved from the Medical Records department of the hospital, and relevant information extracted from the case notes included the demographic characteristics of patients, clinical features at presentation, laboratory investigation results which include peripheral blood film examination result, bone marrow aspiration reports, full blood count results and the FAB classification subtypes of the Acute myeloid leukemia and treatment given were also documented.

The diagnosis of AML in the patients was made based on the clinical and laboratory features at presentation and classification into the various subtypes was done using the FAB Classification method¹⁰ and final diagnosis was arrived at by consensus among the Consultants and Senior Residents in the department.

The data generated from the above sources were entered into Excel Sheet and analyzed using the Statistical Package for the Social Sciences (SSPS) version 21 (IBM Corporation, Armonk, NY, USA) and results were presented in the form of frequency tables.

Results

A total of 46 patients were diagnosed and managed for AML at the center during the study period. There were 24 males and 22 females giving a male: female (M:F) ratio of 1.1:1.

The median age of the patients at diagnosis was 20.6 ± 15.9 years (range = 16 months – 60 years), and the highest prevalence of the disease was found in the 11 – 20 years age group (n = 20, 43.5%), followed by 0 – 10 year age group (n = 13, 28.3%). There were 4 (8.7%) patients in the 51 – 60 years age group. Table 1 shows the age and sex distribution of AML patients in our study.

The most common presenting symptoms were fever (n=, 91.3%), pallor(n=, 84.8%), bleeding diathesis (n=, 52.2%), and body weakness(n=, 45.7%). The most common clinical signs included gum hypertrophy(n=, 30.4%), lymphadenopathy (n=, 23.9%), splenomegaly (n=, 13%) and hepatomegaly (n=, 6.5%). Table 2.

The FAB classification method was used to characterize the patients into the different subtypes of AML, and the commonest subtype of AML in our study was M4 (Acute myelomonocytic leukemia) which was seen in 26 (56.5%) patients, followed by M5 (Acute monocytic leukemia) observed in 10 (21.7%) patients. The other FAB subtypes seen were M1 (n=4, 8.7%), M2 (n= 4, 8.7%) and M3 (n= 2, 4.4%). There were no cases of M0, M6 and M7 recorded in this study. Table 3.

The mean $\pm$ SD values of haematological parameters in the AML patients were PCV ($19.9 \pm 5.8\%$), Hb conc. (6.6 ± 1.9 g/dL), Total WBC ($48.1 \pm 54.8 \times 10^9/L$) and Platelet Count ($39.6 \pm 24.0 \times 10^9/L$). The means $\pm$ SD of percentage of myeloblasts (% blasts) in peripheral blood and bone marrow films were $38.1 \pm 9.3\%$ and $43.5 \pm 15.6\%$ respectively. The diagnosis of AML in our patients was made when 20% myeloblasts were found in both the peripheral blood and bone marrow smears examination, in addition to the morphological characteristics of the myeloblasts. The presence of thrombocytopenia (low platelet count) was the commonest haematological finding in our patients at presentation (n = 44, 95.7%) followed by anaemia (haemoglobin concentration < 10 g/dL) in 39 (84.8%) patients and leucocytosis in 38 (82.6%) patients. Table 4 shows the haematological parameters of the AML patients at diagnosis.

Table 1: Age and Sex distribution of Patients with Acute Myeloid leukemia in Ilorin

Age(Years)	Sex		Total number of patients (%)
	Male	Female	
0 – 10	7	6	13 (28.3)
11 – 20	9	11	20 (43.5)
21 – 30	1	1	2 (4.3)
31 – 40	3	2	5 (10.9)
41 – 50	2	0	2 (4.3)
51 – 60	2	2	4 (8.7)
Total	24	22	46 (100)

Table 2: Frequency (%) distribution of common Clinical features of AML at presentation.

Clinical Features	Number of patients (n)	Percentage (%)
Fever	42	91.3
Pallor	39	84.8
Bleeding diathesis	24	52.2
Body weakness	21	45.7
Bone /Joint Pain	11	23.9
Abdominal pain/swelling	6	13.0
Cough/Dyspnoea	6	13.0
Leg swelling	4	8.7
Weight loss	4	8.7
Jaundice	3	6.5
Gum hypertrophy	14	30.4
Lymphadenopathy	11	23.9
Splenomegaly	6	13.0
Hepatomegaly	3	6.5

Table 3: FAB Classification and frequency of AML subtypes among patients in UITH.

FAB Subtype of AML	Number of patients (n)	Percentage (%)
M0 (AML undifferentiated)	0	0
M1 (AML differentiated, no maturation)	4	8.7
M2 (AML with maturation)	4	8.7
M3 (Acute promyelocytic leukemia)	2	4.4
M4 (Acute myelomonocytic leukemia)	26	56.5
M5 (Acute monocytic leukemia)	10	21.7
M6 (Erythroleukemia)	0	0
M7 (Acute megakaryoblastic leukemia)	0	0
Total	46	100

Table 4: Haematological parameters of AML patients at Diagnosis in UITH.

Parameter	Mean	SD	Range
PCV (%)	19.9	5.8	8 – 34
Haemoglobin concentration (g/dL)	6.6	1.9	2.6 – 10.5
Total White Blood Cell Count (x 10 ⁹ /L)	48.1	54.8	2.5 – 180.6
% Blast in peripheral blood Smear	38.1	9.3	19.2 – 52.5
% Blast in bone marrow Smear	43.5	15.6	21.6 – 58.7
Platelet Count (x 10 ⁹ /L)	39.6	24.0	10 – 122.0

Discussion

Acute myeloid leukemia is a heterogenous malignant haematological disorder which results from clonal proliferation of myeloid precursors in the bone marrow with excessive abnormal accumulation of immature white blood cells (myeloblasts) in blood, bone marrow and tissue infiltration. The clinical features which are observed in patients with AML at presentation are mainly due to the suppression of haemopoietic activities in the bone marrow resulting in bone marrow failure and paucity of mature red blood cells and platelets in circulation, and infiltration of various tissues and organs by the leukemic cells^{1,3}.

Acute myeloid leukemia affects all ages and is found in both sexes but incidence varies in different populations all over the world. There is a male preponderance in the incidence of AML; and though the disease can occur at any age, it has been reported to be more common in the elderly above 60 years of age in the Western countries⁵.

In the present study, AML was found to have the highest prevalence in children and adolescents (0 – 10 and 11 – 20 years age groups) constituting 71.8% of the patients. Similar findings were reported in Ibadan, Nigeria where it was found that the mean age of their AML patients to be 21.4 years, and 56% of their patients were in the 0 – 20 years age bracket. Also, Ramprasanth et al³ in India reported AML to be most prevalent in the 15 – 30 years age group in their study. However, our finding was at variance with the study of Khan which found the highest prevalence of AML in the 60 – 67 years age group¹.

The incidence of haematological malignancies, AML inclusive, is said to be increasing worldwide, and this has been associated with geographical, socio-economic and genetic factors¹³. Given the marked disparity in the physical and social environment between the developed and developing countries, and the increased life expectancy above 70 years in the Western countries, this may possibly account for the higher age at presentation found in studies from the Western countries compared to the much lower age found at presentation in this study^{14,15}.

In our study, a slight male preponderance was observed, the M:F ratio being 1.1:1. This finding was in agreement with M:F ratio reported in similar studies by Arber et al (1.05:1)¹⁶, Harani et al (1.15:1)¹⁷ and Appelbaum et al (1.2:1)¹⁸ but at variance with those reported by Olaniyi et al (2.1:1)⁶, Oyesakin et al (1.5:1)⁷ and Ramprasanth et al (3:1)³.

The most common clinical features at presentation in this study were fever (91.3%), pallor (84.8%), bleeding disorders such as petechial and purpuric rashes, subconjunctival haemorrhage, gum bleeding and menorrhagia (52.2%) and body weakness (45.7%). This finding was similar to the reports by Ramprasanth et al, Preethi CR and Gosh et al^{3,13,19}. Gum hypertrophy, as a result of infiltration of gum by the myeloblasts was documented in 14 (30.4%) patients in our study. Gingival hypertrophy is known to occur more commonly with Monocytic leukemias²⁰ and this finding was found to be consistent with the higher proportion of monocytic subtypes of AML (M4 and M5) recorded in our study. Similar finding was reported in the study by Preethi CR which found gum hypertrophy in 27.2% of patients with M4 and 75% of patients with M5 subtypes¹³, but differs from the report by Khan MI which found gum hypertrophy in only 5% of patients with M4¹.

Also, organ enlargements due to infiltration by the leukemic blasts was observed as lymphadenopathy, splenomegaly and hepatomegaly in 29.3%, 13% and 6.5% of patients respectively. This finding was similar to the report of Khan MI but differs from the studies of Preethi CR and Mathur et al where higher percentage of hepatomegaly and splenomegaly at presentation was reported in their patients^{1,13,21}.

Anaemia and thrombocytopenia are common features in AML, and in the present study, the mean haemoglobin concentration was 6.6 g/dL while the mean platelet count was 39.6 x10⁹/L. These changes in the haematological parameters of AML patients are attributable to the suppression of erythroid and megakaryocytic precursors by the leukemic blasts in the bone marrow resulting in paucity of mature red blood cells and platelets in

circulation¹. The total WBC count was significantly increased (mean = $48.1 \times 10^9/L$), while the mean blast percentage in the peripheral blood (38.1%) and bone marrow (43.5%) smears were equally elevated. In a normal bone marrow, the proportion of blasts to other nucleated marrow cells is less than 5%. But with the uncontrolled proliferation of the malignant white cell precursors in the bone marrow, the immature white cells accumulate in the blood and marrow giving rise to leucocytosis and increased blast count. Similar pattern of changes in the haematological parameters had been reported previously by several authors^{1,5,7,13}.

The FAB classification method is still being used by haematologists in many centres for diagnosis and classification of AML subtypes for prognostic purposes because it is readily available, quick and cost effective when compared with the WHO classification method which requires cytogenetics and molecular studies which may not be readily available in resource-limited settings. AML M4 was the commonest subtype seen in our patients (n = 26, 56.5%), followed by M5 subtype (n = 10, 21.7%). AML M1 and M2 constituted 8.7% each while M3 was seen in 2 (4.4%) patients. There were no patients with M0, M6 and M7 subtypes in our study. This finding is at variance with some previous studies which reported highest prevalence of M2 subtypes^{1,13} and M1²². The different subtypes of AML are associated with different prognosis and it is of utmost importance to determine the correct FAB subtype at diagnosis. While AML M0, M1, M6 and M7 are associated with poor prognosis, the FAB subtypes M2, M3 and M4 have good prognostic value^{1,21}.

Conclusion

In the index study, the diagnosis of AML was made based on the clinical presentation and laboratory features of the disease. There were no facilities for cytogenetics or molecular diagnosis. Since many centres in Nigeria and other resource limited countries still rely to a large extent on the clinical features and routine haematological tests for diagnosis, treatment and follow-up of patients with AML, it is imperative for Haemato-oncologists and other clinicians to be conversant with these clinical features and laboratory investigations for prompt referral, diagnosis and management of patients with the disease in our environment.

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